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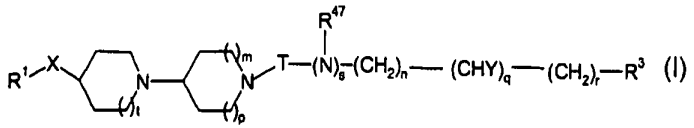
(54) Title: CHEMICAL COMPOUNDS



(57) Abstract: The present invention provides a compound of a formula (I) wherein the variables are defined herein; to a process for preparing such a compound; and to the use of such a compound in the treatment of a chemokine (such as CCR3) or H1 mediated disease state.

CHEMICAL COMPOUNDS

The present invention concerns piperidine derivatives having pharmaceutical activity, to processes for preparing such derivatives, to pharmaceutical compositions comprising such derivatives and to the use of such derivatives as active therapeutic agents.

Pharmaceutically active piperidine derivatives are disclosed in WO99/38514, WO99/04794 and WO00/35877.

Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T cells, eosinophils, basophils and neutrophils to sites of inflammation and also play a rôle in the maturation of cells of the immune system. Chemokines play an important role in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C, or α) and Cys-Cys (C-C, or β) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β).

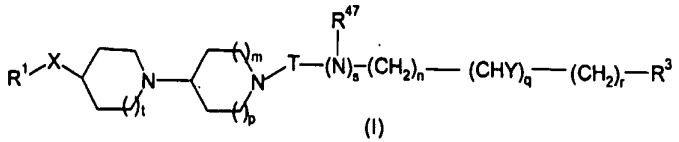
Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3 and CXCR4. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

Histamine is a basic amine, 2-(4-imidazolyl)-ethylamine, and is formed from histidine by histidine decarboxylase. It is found in most tissues of the body, but is present

in high concentrations in the lung, skin and in the gastrointestinal tract. At the cellular level inflammatory cells such as mast cells and basophils store large amounts of histamine. It is recognised that the degranulation of mast cells and basophils and the subsequent release of histamine is a fundamental mechanism responsible for the clinical manifestation of an allergic process. Histamine produces its actions by an effect on specific histamine G-protein coupled receptors, which are of three main types, H1, H2 and H3. Histamine H1 antagonists comprise the largest class of medications used in the treatment of patients with allergic disorders, especially rhinitis and urticaria. H1 antagonists are useful in controlling the allergic response by for example blocking the action of histamine on post-capillary venule smooth muscle, resulting in decreased vascular permeability, exudation and oedema. The antagonists also produce blockade of the actions of histamine on the H1 receptors on c-type nociceptive nerve fibres, resulting in decreased itching and sneezing.

Viral infections are known to cause lung inflammation. It has been shown experimentally that the common cold increases mucosal output of eotaxin in the airways. Instillation of eotaxin into the nose can mimic some of the signs and symptoms of a common cold. (See, Greiff L *et al* Allergy (1999) 54(11) 1204-8 [Experimental common cold increase mucosal output of eotaxin in atopic individuals] and Kawaguchi M *et al* Int. Arch. Allergy Immunol. (2000) 122 S1 44 [Expression of eotaxin by normal airway epithelial cells after virus A infection].)

The present invention provides a compound of formula (I):



(I)

wherein:

q, s and t are, independently, 0 or 1;

n and r are, independently, 0, 1, 2, 3, 4 or 5;

m and p are, independently, 0, 1 or 2;

X is CH_2, C(O), O, S, S(O), $S(O)_2$ or NR^{37}; provided that when m and p are both 1 then X is not CH_2;

Y is NHR^2 or OH;

T is C(O), C(S), $S(O)_2$ or CH_2;

R^1 is hydrogen, C_{1-6} alkyl, aryl or heterocyclyl;

R^2 and R^{47} are, independently, hydrogen, C_{1-6} alkyl, aryl(C_{1-4})alkyl or CO(C_{1-6} alkyl);

R^3 is C_{1-6} alkyl {optionally substituted by halogen, CO_2R^4 or phthalimide}, $CR^{3a}R^{3b}R^{3c}$, C_{2-4} alkenyl {optionally substituted by aryl or heterocyclyl}, C_{3-7} cycloalkyl {optionally substituted by C_{1-4} alkyl, aryl or oxo}, C_{3-7} cycloalkenyl {optionally substituted by oxo, C_{1-6} alkyl or aryl}, aryl, heterocyclyl, thioaryl or thioheterocyclyl;

R^{3a} is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy or C_{3-7} cycloalkyl; R^{3b} is aryl, heterocyclyl, $S(O)_2$aryl or $S(O)_2$heterocyclyl; and R^{3c} is C_{1-6} alkyl, C_{1-4} haloalkyl, hydroxy, heterocyclyl(C_{1-4} alkyl) or aryl;

wherein, unless stated otherwise, the foregoing aryl and heterocyclyl moieties are optionally substituted by: halogen, OH, SH, NO_2, oxo, C_{1-6} alkyl {itself optionally substituted by halogen, $OC(O)C_{1-6}$ alkyl, $S(O)_2R^{48}$, phenyl (itself optionally substituted by halogen (such as one or two chlorine or fluorine atoms), C_{1-6} alkyl, $S(O)_2R^{38}$ or $C(O)NR^{39}R^{40}$), naphthyloxy (itself optionally substituted by halo or C_{2-6} alkenyl), C_{3-10} cycloalkyl (itself optionally substituted by C_{1-4} alkyl or oxo) or $NR^{41}C(O)OCH_2$(fluoren-9-yl)}, $NR^{41}C(O)OCH_2$(fluoren-9-yl), C_{1-6} alkoxy {itself optionally substituted by halogen, C_{1-6} alkoxy, $NHCO_2(C_{1-6}$ alkyl), CO_2R^4, NR^5R^6 or phenyl (itself optionally substituted by halogen or NO_2)}, C_{1-6} alkylthio, C_{1-6} haloalkylthio, C_{3-10} cycloalkyl, NR^7R^8, $NR^9C(O)R^{10}$, CO_2R^{11}, $C(O)NR^{12}R^{13}$, $C(O)R^{14}$, $S(O)_dR^{15}$, $S(O)_2NR^{42}R^{43}$, $NR^{44}S(O)_2R^{45}$, phenyl {itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy (itself optionally substituted by halogen, OH or pyridinyl), phenyl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy) or heterocyclyl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy)}, heterocyclyl {itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy, C_{1-6} haloalkoxy, phenyl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy) or heterocyclyl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy)}, phenoxy {itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy, C_{1-6} haloalkoxy, phenyl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy) or heterocyclyl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy)}, SCN, CN, SO_3H (or an alkali metal salt thereof), methylenedioxy or difluoromethylenedioxy; when aryl is phenyl adjacent substituents may

join to form, together with the phenyl ring to which they are attached, a dihydrophenanthrene moiety;

d is 0, 1 or 2;

R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{37}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43} and R^{44} are, independently, hydrogen, C_{1-6} alkyl, aryl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy) or heterocyclyl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy);

R^{15}, R^{38}, R^{45} and R^{48} are, independently, C_{1-6} alkyl (optionally substituted by halogen, hydroxy or C_{3-10} cycloalkyl), C_{3-6} alkenyl, aryl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy) or heterocyclyl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy);

or an N-oxide thereof; or a pharmaceutically acceptable salt thereof; or a solvate thereof;

provided that:

when m and p are both 1, n, q and r are all 0, T and X are both $S(O)_2$, and R^1 is methoxyphenyl then R^3 is not propyl; when m, p, q and r are all 1, n is 0, Y is NH_2, T is CO and R^1X is $(CH_3)_2N$ then R^3 is not 3,5-dibromo-4-aminophenyl, 1-methylindol-3-yl or 1-(tert-butoxycarbonyl)indol-3-yl; and when m and p are both 1, n, q and r are all 0, T is CO, X is NH and R^1 is 3-(4-fluorobenzyl)benzimidazol-2-yl then R^3 is not 4-fluorophenyl.

Certain compounds of the present invention can exist in different isomeric forms (such as enantiomers, diastereomers, geometric isomers or tautomers). The present invention covers all such isomers and mixtures thereof in all proportions.

Suitable salts include acid addition salts such as a hydrochloride, dihydrochloride, hydrobromide, phosphate, acetate, diacetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate. Another example of an addition salt is sulphate.

The compounds of the invention may exist as solvates (such as hydrates) and the present invention covers all such solvates.

Halogen includes fluorine, chlorine, bromine and iodine.

Alkyl groups and moieties are straight or branched chain and are, for example, methyl, ethyl, n-propyl, iso-propyl or tert-butyl.

Alkenyl group are, for example, vinyl or allyl.

Cycloalkyl is mono-, bi or tricyclic and is, for example, cyclopropyl, cyclopentyl, cyclohexyl, norbornyl or camphoryl. The cycloalkyl ring is optionally fused to a benzene ring (for example forming a bicyclo[4.2.0]octa-1,3,5-trienyl or indanyl ring system).

Cycloalkenyl is especially monocyclic and is, for example, cyclopentenyl or cyclohexenyl.

Aryl is preferably phenyl or naphthyl.

Heterocyclyl is an aromatic or non-aromatic 5 or 6 membered ring, optionally fused to one or more other rings, comprising at least one heteroatom selected from the group comprising nitrogen, oxygen and sulphur; or an N-oxide thereof, or an S-oxide or S-dioxide thereof. Heterocyclyl is, for example, furyl, thienyl (also known as thiophenyl), pyrrolyl, 2,5-dihydropyrrolyl, thiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, piperidinyl, morpholinyl, pyridinyl (for example in 6-oxo-1,6-dihydro-pyridinyl), pyrimidinyl, indolyl, 2,3-dihydroindolyl, benzo[b]furyl (also known as benzfuryl), benz[b]thienyl (also known as benzthienyl or benzthiophenyl), 2,3-dihydrobenz[b]thienyl (for example in 1-dioxo-2,3-dihydrobenz[b]thienyl), indazolyl, benzimidazolyl, benztriazolyl, benzoxazolyl, benzthiazolyl (for example in 1H-benzthiazol-2-one-yl), 2,3-dihydrobenzthiazolyl (for example in 2,3-dihydrobenzthiazol-2-one-yl), 1,2,3-benzothiadiazolyl, an imidazopyridinyl (such as imidazo[1,2a]pyridinyl), thieno[3,2-b]pyridin-6-yl 1,2,3-benzoxadiazolyl (also known as benzo[1,2,3]thiadiazolyl), 2,1,3-benzothiadiazolyl, benzofurazan (also known as 2,1,3-benzoxadiazolyl), quinoxalinyl, dihydro-1-benzopyryliumyl (for example in a coumarinyl or a chromonyl), 3,4-dihydro-1H-2,1-benzothiazinyl (for example in 2-dioxo-3,4-dihydro-1H-2,1-benzothiazinyl), a pyrazolopyridine (for example 1H-pyrazolo[3,4-b]pyridinyl), a purine (for example in 3,7-dihydro-purin-2,6-dione-8-yl), quinolinyl, isoquinolinyl (for example in 2H-isoquinolin-1-one-yl), a naphthyridinyl (for example [1,6]naphthyridinyl or [1,8]naphthyridinyl or in 1H-[1,8]naphthyridin-4-one-yl), a benzothiazinyl (for example in 4H-benzo[1,4]thiazin-3-one-yl), benzo[d]imidazo[2,1-b]thiazol-2-yl or dibenzothiophenyl (also known as dibenzothienyl); or an N-oxide thereof, or an S-oxide or S-dioxide thereof.

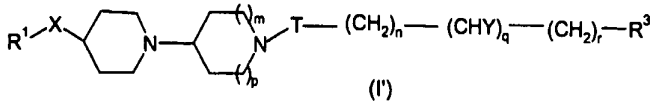
In one aspect of the invention heterocyclyl is an aromatic or non-aromatic 5 or 6 membered ring, optionally fused to one or more other rings, comprising at least one heteroatom selected from the group comprising nitrogen, oxygen and sulphur. Heterocyclyl is, for example, furyl, thienyl, 2,1,3-benzothiadiazole, 2,1,3-benzoxadiazole, quinoxaline, dihydro-1-benzopyrylium (for example a coumarin or a chromone),

piperidine, morpholine, pyrrole, indole, 2,3-dihydroindole, quinoline, thiazole, pyrazole, isoxazole, imidazole, pyridine, benzofuryl, benzimidazole, pyrimidine or dibenzothiophene.

In a further aspect heterocyclyl is an aromatic or non-aromatic 5 or 6 membered ring, optionally fused to one or more other rings, comprising at least one heteroatom selected from the group comprising nitrogen, oxygen and sulphur; or an N-oxide thereof, or an S-oxide or S-dioxide thereof. Heterocyclyl is, for example, furyl, thienyl (also known as thiophenyl), pyrrolyl, 2,5-dihydropyrrolyl, thiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, piperidinyl, morpholinyl, pyridinyl, pyrimidinyl, indolyl, 2,3-dihydroindolyl, benzo[b]furyl (also known as benzfuryl), benz[b]thienyl (also known as benzthienyl or benzthiophenyl), 2,3-dihydrobenz[b]thienyl (for example 1-dioxo-2,3-dihydrobenz[b]thienyl), benzimidazolyl, benztriazolyl, benzoxazolyl, benzthiazolyl, 2,3-dihydrobenzthiazolyl (for example 2,3-dihydrobenzthiazol-2-onyl), 1,2,3-benzothiadiazolyl, 1,2,3-benzoxadiazolyl (also known as benzo[1,2,3]thiadiazolyl), 2,1,3-benzothiadiazolyl, benzofurazan (also known as 2,1,3-benzoxadiazolyl), quinoxalinyl, dihydro-1-benzopyryliumyl (for example a coumarinyl or a chromonyl), 3,4-dihydro-1H-2,1-benzothiazinyl (for example 2-dioxo-3,4-dihydro-1H-2,1-benzothiazinyl), quinolinyl, isoquinolinyl or dibenzothiophenyl (also known as dibenzothienyl); or an N-oxide thereof, or an S-oxide or S-dioxide thereof.

An N-oxide of a compound of formula (I) is, for example, a 1-oxy-[1,4']bipiperidinyl-1'-yl compound.

In another aspect the present invention provides a compound of formula (I'):



(I')

wherein: q is 0 or 1; n and r are, independently, 0, 1, 2, 3, 4 or 5; m and p are, independently, 0, 1 or 2; X is CH_2, CO, O, S, S(O), $S(O)_2$ or NR^{37}; provided that when m and p are both 1 then X is not CH_2; Y is NHR^2 or OH; T is CO, CS, SO_2 or CH_2; R^1 is hydrogen, C_{1-6} alkyl, aryl or heterocyclyl; R^2 is hydrogen, C_{1-6} alkyl, aryl(C_{1-4})alkyl or CO(C_{1-6} alkyl); R^3 is C_{1-6} alkyl {optionally substituted by halogen, CO_2R^4 or phthalimide}, C_{3-7} cycloalkyl {optionally substituted by C_{1-4} alkyl or oxo}, C_{3-7} cycloalkenyl {optionally substituted by C_{1-6} alkyl or aryl}, aryl or heterocyclyl; wherein, unless stated otherwise, the foregoing aryl and heterocyclyl moieties are optionally substituted by: halogen, OH, SH,

NO_2, oxo, C_{1-6} alkyl (itself optionally substituted by halogen, $OC(O)C_{1-6}$ alkyl, phenyl (itself optionally substituted by halo (such as one or two chlorine or fluorine atoms), C_{1-6} alkyl, SO_2R^{38} or $CONR^{39}R^{40}$), naphthyloxy (itself optionally substituted by halo or C_{2-6} alkenyl) or $NR^4C(O)OCH_2$(fluoren-9-yl)), $NR^{41}C(O)OCH_2$(fluoren-9-yl), C_{1-6} alkoxy (itself optionally substituted by halogen, CO_2R^4, NR^5R^6 or phenyl (itself optionally substituted by halogen or NO_2)), C_{1-6} alkylthio, nitro, C_{3-7} cycloalkyl, NR^7R^8, NR^9COR^{10}, CO_2R^{11}, $CONR^{12}R^{13}$, COR^{14}, SO_dR^{15}, $SO_2NR^{42}R^{43}$, $NR^{44}SO_2R^{45}$, phenyl (itself optionally substituted by halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2 or C_{1-6} alkoxy (itself optionally substituted by halo, OH or pyridinyl)), heterocyclyl (itself optionally substituted by halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy), phenoxy (itself optionally substituted by halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy), SCN, CN, SO_3H (or an alkali metal salt thereof) or methylenedioxy; when aryl is phenyl adjacent substituents may join to form, together with the phenyl ring to which they are attached, a dihydrophenanthrene moiety; d is 0, 1 or 2; R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{37}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43} and R^{44} are, independently, hydrogen, C_{1-6} alkyl or aryl (itself optionally substituted by halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy); R^{15}, R^{38} and R^{45} are, independently, C_{1-6} alkyl or aryl (itself optionally substituted by halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy); or a pharmaceutically acceptable salt thereof; or a solvate thereof; provided that: when m and p are both 1, n, q and r are all 0, T and X are both SO_2, and R^1 is methoxyphenyl then R^3 is not propyl; when m, p, q and r are all 1, n is 0, Y is NH_2, T is CO and R^1X is $(CH_3)_2N$ then R^3 is not 3,5-dibromo-4-aminophenyl, 1-methylindol-3-yl or 1-(tert-butoxycarbonyl)indol-3-yl; and when m and p are both 1, n, q and r are all 0, T is CO, X is NH and R^1 is 3-(4-fluorobenzyl)benzimidazol-2-yl then R^3 is not 4-fluorophenyl.

In an further aspect the present invention provides a compound of formula (I), wherein: q, s and t are, independently, 0 or 1; n and r are, independently, 0, 1, 2, 3, 4 or 5; m and p are, independently, 0, 1 or 2; X is CH_2, C(O), O, S, S(O), $S(O)_2$ or NR^{37}; provided that when m and p are both 1 then X is not CH_2; Y is NHR^2 or OH; T is C(O), C(S), $S(O)_2$ or CH_2; R^1 is hydrogen, C_{1-6} alkyl, aryl or heterocyclyl; R^2 and R^{47} are, independently, hydrogen, C_{1-6} alkyl, aryl(C_{1-4})alkyl or CO(C_{1-6} alkyl); R^3 is C_{1-6} alkyl {optionally substituted by halogen, CO_2R^4 or phthalimide}, C_{3-7} cycloalkyl {optionally substituted by C_{1-4} alkyl or oxo}, C_{3-7} cycloalkenyl {optionally substituted by oxo, C_{1-6} alkyl or aryl}, aryl or heterocyclyl; wherein, unless stated otherwise, the foregoing aryl and heterocyclyl

moieties are optionally substituted by: halogen, OH, SH, NO_2, oxo, C_{1-6} alkyl (itself optionally substituted by halogen, $OC(O)C_{1-6}$ alkyl, $S(O)_2R^{48}$, phenyl (itself optionally substituted by halo (such as one or two chlorine or fluorine atoms), C_{1-6} alkyl, $S(O)_2R^{38}$ or $C(O)NR^{39}R^{40}$), naphthyloxy (itself optionally substituted by halo or C_{2-6} alkenyl), C_{3-10} cycloalkyl (itself optionally substituted by C_{1-4} alkyl or oxo) or $NR^{41}C(O)OCH_2$(fluoren-9-yl)), $NR^{41}C(O)OCH_2$(fluoren-9-yl), C_{1-6} alkoxy (itself optionally substituted by halogen, C_{1-6} alkoxy, $NHCO_2(C_{1-6}$ alkyl), CO_2R^4, NR^5R^6 or phenyl (itself optionally substituted by halogen or NO_2)), C_{1-6} alkylthio, C_{1-6} haloalkylthio, C_{3-10} cycloalkyl, NR^7R^8, $NR^9C(O)R^{10}$, CO_2R^{11}, $C(O)NR^{12}R^{13}$, $C(O)R^{14}$, $S(O)_dR^{15}$, $S(O)_2NR^{42}R^{43}$, $NR^{44}S(O)_2R^{45}$, phenyl (itself optionally substituted by halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2 or C_{1-6} alkoxy (itself optionally substituted by halo, OH or pyridinyl)), heterocyclyl (itself optionally substituted by halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy), phenoxy (itself optionally substituted by halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy), SCN, CN, SO_3H (or an alkali metal salt thereof) or methylenedioxy; when aryl is phenyl adjacent substituents may join to form, together with the phenyl ring to which they are attached, a dihydrophenanthrene moiety; d is 0, 1 or 2; R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{37}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43} and R^{44} are, independently, hydrogen, C_{1-6} alkyl or aryl (itself optionally substituted by halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy); R^{15}, R^{38}, R^{45} and R^{48} are, independently, C_{1-6} alkyl (optionally substituted by halogen, hydroxy or C_{3-10} cycloalkyl) or aryl (itself optionally substituted by halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy); or a pharmaceutically acceptable salt thereof; or a solvate thereof; provided that: when m and p are both 1, n, q and r are all 0, T and X are both $S(O)_2$, and R^1 is methoxyphenyl then R^3 is not propyl; when m, p, q and r are all 1, n is 0, Y is NH_2, T is CO and R^1X is $(CH_3)_2N$ then R^3 is not 3,5-dibromo-4-aminophenyl, 1-methylindol-3-yl or 1-(tert-butoxycarbonyl)indol-3-yl; and when m and p are both 1, n, q and r are all 0, T is CO, X is NH and R^1 is 3-(4-fluorobenzyl)benzimidazol-2-yl then R^3 is not 4-fluorophenyl.

In another aspect the variables m and p are such that m + p is 0, 1 or 2 (for example 1 or 2).

In a further aspect n is 0 or 1.

In a still further aspect q and r are both 0.

In another aspect n, q and r are all 0.

In another aspect m, p and t are all 1.

In a further aspect s is 0.

In another aspect s is 1. In a further aspect q is 1. In a still further aspect n + r is equal to more than 1 (for example n + r is equal to 2, 3, 4 or 5).

In another aspect t + m + p is not equal to 3 (for example t + m + p is equal to 2).

In a still further aspect X is O.

In another aspect R^1 is hydrogen, C_{1-6} alkyl, optionally substituted (as above) aryl or optionally substituted (as above) monocyclic heterocyclyl. In another aspect R^1 is phenyl substituted with one or more of fluorine, chlorine, C_{1-4} alkyl (especially methyl) or C_{1-4} alkoxy (especially methoxy).

In yet another aspect R^1 is not phenyl substituted by cycloalkyl.

In a further aspect R^1 is phenyl optionally substituted (for example with one, two or three) by halo (especially fluoro or chloro), C_{1-4} alkyl (especially methyl) or C_{1-4} alkoxy (especially methoxy). In a still further aspect R^1 is phenyl substituted by one, two or three of: fluoro, chloro, methyl or methoxy.

In another aspect R^1 is one of the substituted phenyl groups exemplified in Method F below.

In a further aspect T is C(O), $S(O)_2$ or CH_2. In a still further aspect T is C(O). In another aspect T is $S(O)_2$ or CH_2.

In another aspect R^3 is aryl or heterocyclyl either of which is optionally substituted as described above.

In a further aspect R^3 is unsubstituted phenyl, mono-substituted phenyl or mono-substituted heterocyclyl, the substituents being chosen from those described above.

In a still further aspect R^3 is oxo substituted heterocyclyl, said heterocyclyl optionally further substituted with one or more substituents chosen from those described above.

In another aspect R^3 is a bicyclic heterocyclyl optionally substituted as described above. Bicyclic heterocyclyl is an aromatic or non-aromatic 5 or 6 membered ring, fused to one or more other rings, comprising at least one heteroatom selected from the group comprising nitrogen, oxygen and sulphur; or an N-oxide thereof, or an S-oxide or S-dioxide thereof. Bicyclic heterocyclyl is, for example, indolyl, 2,3-dihydroindolyl, benzo[b]furyl (also known as benzfuryl), benz[b]thienyl (also known as benzthienyl or benzthiophenyl), 2,3-dihydrobenz[b]thienyl (for example in 1-dioxo-2,3-dihydrobenz[b]thienyl), indazolyl, benzimidazolyl, benztriazolyl, benzoxazolyl,

benzthiazolyl (for example in 1H-benzthiazol-2-one-yl), 2,3-dihydrobenzthiazolyl (for example in 2,3-dihydrobenzthiazol-2-one-yl), 1,2,3-benzothiadiazolyl, an imidazopyridinyl (such as imidazo[1,2a]pyridinyl), thieno[3,2-b]pyridin-6-yl 1,2,3-benzoxadiazolyl (also known as benzo[1,2,3]thiadiazolyl), 2,1,3-benzothiadiazolyl, benzofurazan (also known as 2,1,3-benzoxadiazolyl), quinoxalinyl, dihydro-1-benzopyryliumyl (for example in a coumarinyl or a chromonyl), 3,4-dihydro-1H-2,1-benzothiazinyl (for example in 2-dioxo-3,4-dihydro-1H-2,1-benzothiazinyl), a pyrazolopyridine (for example 1H-pyrazolo[3,4-b]pyridinyl), a purine (for example in 3,7-dihydro-purin-2,6-dione-8-yl), quinolinyl, isoquinolinyl (for example in 2H-isoquinolin-1-one-yl), a naphthyridinyl (for example [1,6]naphthyridinyl or [1,8]naphthyridinyl or in 1H-[1,8]naphthyridin-4-one-yl) or a benzothiazinyl (for example in 4H-benzo[1,4]thiazin-3-one-yl); or an N-oxide thereof, or an S-oxide or S-dioxide thereof.

In yet another aspect R^3 is: C_{1-6} alkyl {optionally substituted by CO_2R^{16} or phthalimide}, C_{3-7} cycloalkyl {optionally substituted by oxo}, phenyl {optionally substituted by: halogen, OH, SH, C_{1-6} alkyl (itself optionally substituted by naphthyloxy (itself optionally substituted by halo or alkenyl) or $NR^{17}C(O)OCH_2$(fluoren-9-yl)), C_{1-6} alkoxy (itself optionally substituted by CO_2R^{18}, $NR^{19}R^{20}$ or phenyl (itself optionally substituted by halogen or NO_2)), C_{1-6} alkylthio, C_{1-4} haloalkyl, OCF_3, nitro, C_{3-7} cycloalkyl, $NR^{21}R^{22}$, $NR^{23}C(O)R^{24}$, CO_2R^{25}, $C(O)NR^{26}R^{27}$, $S(O)_2R^{28}$, phenyl (itself optionally substituted by NO_2 or alkoxy (itself optionally substituted by OH or pyridinyl)), phenoxy, SCN, CN, SO_3H (or an alkali metal salt thereof) or methylenedioxy, or adjacent substituents may join to form a dihydrophenanthrene moiety}, naphthyl {optionally substituted by $NR^{29}R^{30}$ or OH}, heterocyclyl {optionally substituted by halo, NO_2, oxo, C_{1-6} alkyl (itself optionally substituted by $OC(O)C_{1-6}$ alkyl, phenyl (itself optionally substituted by halo or alkyl)), alkoxy, CF_3, thioalkyl, $C(O)R^{31}$, CO_2R^{32}, $NR^{33}C(O)R^{34}$, phenoxy, phenyl or nitrogen containing heterocyclyl;

R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33} and R^{34} are, independently, hydrogen, C_{1-6} alkyl or phenyl;

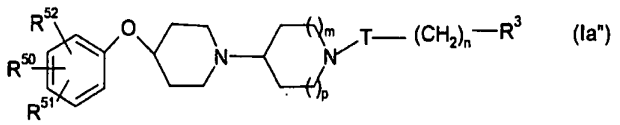
R^{28} is C_{1-6} alkyl; or a pharmaceutically acceptable salt thereof.

In another aspect R^3 is phenyl or heterocyclyl, either of which is optionally substituted by: halo, hydroxy, nitro, cyano, amino, C_{1-4} alkyl (itself optionally substituted by $S(O)_2(C_{1-4}$ alkyl), $S(O)_2$phenyl), C_{1-4} alkoxy, $S(O)_kR^{46}$ (wherein k is 0, 1 or 2 (preferably 2); and R^{46} is C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{3-7} cycloalkyl(C_{1-4} alkyl) (such as cyclopropylmethyl) or phenyl), C_{1-4} haloalkylthio, $C(O)NH_2$, $NHS(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl) or $S(O)_2N(C_{1-4}$ alkyl)$_2$.

In one aspect the variable R^3 can be benzo[1,2,3]thiadiazolyl, thiophenyl or phenyl; the phenyl and thiophenyl rings being optionally substituted by: halo, hydroxy, nitro, cyano, amino, C_{1-4} alkyl (itself optionally substituted by $S(O)_2(C_{1-4}$ alkyl), $S(O)_2$phenyl), C_{1-4} alkoxy, $S(O)_kR^{46}$ (wherein k is 0, 1 or 2 (preferably 2); and R^{46} is C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{3-7} cycloalkyl(C_{1-4} alkyl) (such as cyclopropylmethyl) or phenyl), C_{1-4} haloalkylthio, $C(O)NH_2$, $NHS(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl) or $S(O)_2N(C_{1-4}$ alkyl)$_2$.

In another aspect the variable R^3 can be benzo[1,2,3]thiadiazolyl or phenyl (optionally substituted by: halo, hydroxy, nitro, cyano, amino, C_{1-4} alkyl (itself optionally substituted by $S(O)_2$phenyl), C_{1-4} alkoxy, $S(O)_kR^{46}$ (wherein k is 0, 1 or 2; and R^{46} is C_{1-4} alkyl or phenyl) or C_{1-4} haloalkylthio.

In a still further aspect the present invention provides a compound of formula (Ia''):



(Ia'')

wherein:

T is C(O), C(S), $S(O)_2$ or CH_2;

n is 0, 1, 2, 3, 4 or 5;

m and p are, independently, 0, 1 or 2 (but are especially both 1);

R^{50} is hydrogen, cyano, $S(O)_2(C_{1-4}$ alkyl), $S(O)_2(C_{1-4}$ haloalkyl), halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy or phenyl (optionally substituted by one or two halogen atoms or by one $C(O)NR^{12'}R^{13'}$, $NR^{9'}C(O)R^{10'}$, $S(O)_2R^{15'}$, $S(O)_2NR^{42}R^{43}$ or $NR^{44}S(O)_2R^{45}$ group);

R^{51} and R^{52} are, independently, hydrogen, halogen, C_{1-4} alkyl or C_{1-4} alkoxy;

R^3 is C_{1-6} alkyl {optionally substituted by halogen, CO_2R^4 or phthalimide}, C_{3-7} cycloalkyl {optionally substituted by C_{1-4} alkyl or oxo}, aryl or heterocyclyl;

wherein, unless stated otherwise, the foregoing aryl and heterocyclyl moieties are optionally substituted by: halogen, OH, SH, NO_2, oxo, C_{1-6} alkyl (itself optionally substituted by halogen, $OC(O)C_{1-6}$ alkyl, phenyl (itself optionally substituted by halo or C_{1-6} alkyl), naphthyloxy (itself optionally substituted by halo or C_{2-6} alkenyl) or $NR^4C(O)OCH_2$(fluoren-9-yl)), C_{1-6} alkoxy (itself optionally substituted by halogen,

CO_2R^4, NR^5R^6 or phenyl (itself optionally substituted by halogen or NO_2)), C_{1-6} alkylthio, nitro, C_{3-7} cycloalkyl, NR^7R^8, $NR^9C(O)R^{10}$, CO_2R^{11}, $C(O)NR^{12}R^{13}$, $C(O)R^{14}$, $S(O)_2R^{15}$, phenyl (itself optionally substituted by NO_2 or C_{1-6} alkoxy (itself optionally substituted by OH or pyridinyl)), phenoxy, SCN, CN, SO_3H (or an alkali metal salt thereof) or methylenedioxy; when aryl is phenyl adjacent substituents may join to form, together with the phenyl ring a dihydrophenanthrene moiety;

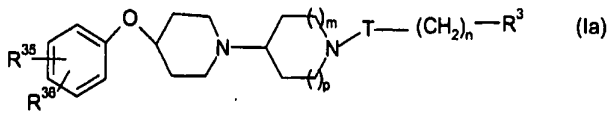
R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, R^{10}, $R^{10'}$, R^{11}, R^{12}, $R^{12'}$, R^{13}, $R^{13'}$, R^{14}, R^{42}, R^{43} and R^{44} are, independently, hydrogen, C_{1-6} alkyl or phenyl;

R^{15}, $R^{15'}$ and R^{45} are, independently, C_{1-6} alkyl or phenyl;

or a pharmaceutically acceptable salt thereof.

In a further aspect R^{50}, R^{51} and R^{52} are, independently, hydrogen, halogen, (especially fluoro or chloro), C_{1-4} alkyl (especially methyl) or C_{1-4} alkoxy (especially methoxy).

In a still further aspect the present invention provides a compound of formula (Ia):



(Ia)

wherein:

T is C(O), C(S), $S(O)_2$ or CH_2;

n is 0, 1, 2, 3, 4 or 5;

m and p are, independently, 0, 1 or 2 (but are especially both 1);

R^{35} is hydrogen, cyano, $S(O)_2(C_{1-4}$ alkyl), $S(O)_2(C_{1-4}$ haloalkyl), halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy or phenyl (optionally substituted by one or two halogen atoms or by one $C(O)NR^{12'}R^{13'}$, $NR^{9'}C(O)R^{10'}$, $S(O)_2R^{15'}$, $S(O)_2NR^{42}R^{43}$ or $NR^{44}S(O)_2R^{45}$ group);

R^{36} is hydrogen, halogen or C_{1-4} alkyl;

R^3 is C_{1-6} alkyl {optionally substituted by halogen, CO_2R^4 or phthalimide}, C_{3-7} cycloalkyl {optionally substituted by C_{1-4} alkyl or oxo}, aryl or heterocyclyl;

wherein, unless stated otherwise, the foregoing aryl and heterocyclyl moieties are optionally substituted by: halogen, OH, SH, NO_2, oxo, C_{1-6} alkyl (itself optionally substituted by halogen, $OC(O)C_{1-6}$ alkyl, phenyl (itself optionally substituted by halo or C_{1-6} alkyl), naphthyloxy (itself optionally substituted by halo or C_{2-6} alkenyl) or $NR^4C(O)OCH_2$(fluoren-9-yl)), C_{1-6} alkoxy (itself optionally substituted by halogen,

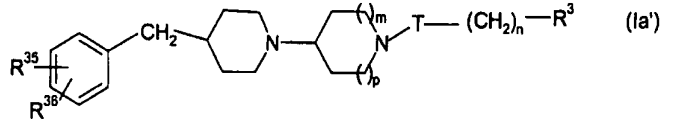
CO_2R^4, NR^5R^6 or phenyl (itself optionally substituted by halogen or NO_2)), C_{1-6} alkylthio, nitro, C_{3-7} cycloalkyl, NR^7R^8, $NR^9C(O)R^{10}$, CO_2R^{11}, $C(O)NR^{12}R^{13}$, $C(O)R^{14}$, $S(O)_2R^{15}$, phenyl (itself optionally substituted by NO_2 or C_{1-6} alkoxy (itself optionally substituted by OH or pyridinyl)), phenoxy, SCN, CN, SO_3H (or an alkali metal salt thereof) or methylenedioxy; when aryl is phenyl adjacent substituents may join to form, together with the phenyl ring a dihydrophenanthrene moiety;

R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, R^{10}, $R^{10'}$, R^{11}, R^{12}, $R^{12'}$, R^{13}, $R^{13'}$, R^{14}, R^{42}, R^{43} and R^{44} are, independently, hydrogen, C_{1-6} alkyl or phenyl;

R^{15}, $R^{15'}$ and R^{45} are, independently, C_{1-6} alkyl or phenyl;

or a pharmaceutically acceptable salt thereof.

In another aspect the present invention provides a compound of formula (Ia'):



(Ia')

wherein:

T is CO, CS, SO_2 or CH_2;

n is 0, 1, 2, 3, 4 or 5;

m and p are, independently, 0, 1 or 2 (but are especially both 1);

R^{35} is hydrogen, cyano, $SO_2(C_{1-4}$ alkyl), $SO_2(C_{1-4}$ haloalkyl), halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy or phenyl (optionally substituted by one or two halogen atoms or by one $CONR^{12'}R^{13'}$, $NR^{9'}COR^{10'}$, $SO_2R^{15'}$, $SO_2NR^{42}R^{43}$ or $NR^{44}SO_2R^{45}$ group);

R^{36} is hydrogen, halogen or C_{1-4} alkyl;

R^3 is C_{1-6} alkyl {optionally substituted by halogen, CO_2R^4 or phthalimide}, C_{3-7} cycloalkyl {optionally substituted by C_{1-4} alkyl or oxo}, aryl or heterocyclyl;

wherein, unless stated otherwise, the foregoing aryl and heterocyclyl moieties are optionally substituted by: halogen, OH, SH, NO_2, oxo, C_{1-6} alkyl (itself optionally substituted by halogen, $OC(O)C_{1-6}$ alkyl, phenyl (itself optionally substituted by halo or C_{1-6} alkyl), naphthyloxy (itself optionally substituted by halo or C_{2-6} alkenyl) or $NR^4C(O)OCH_2$(fluoren-9-yl)), C_{1-6} alkoxy (itself optionally substituted by halogen, CO_2R^4, NR^5R^6 or phenyl (itself optionally substituted by halogen or NO_2)), C_{1-6} alkylthio, nitro, C_{3-7} cycloalkyl, NR^7R^8, NR^9COR^{10}, CO_2R^{11}, $CONR^{12}R^{13}$, COR^{14}, SO_2R^{15}, phenyl (itself optionally substituted by NO_2 or C_{1-6} alkoxy (itself optionally substituted by OH or

pyridinyl)), phenoxy, SCN, CN, SO_3H (or an alkali metal salt thereof) or methylenedioxy; when aryl is phenyl adjacent substituents may join to form, together with the phenyl ring a dihydrophenanthrene moiety;

R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, R^{10}, $R^{10'}$, R^{11}, R^{12}, $R^{12'}$, R^{13}, $R^{13'}$, R^{14}, R^{42}, R^{43} and R^{44} are, independently, hydrogen, C_{1-6} alkyl or phenyl;

R^{15}, $R^{15'}$ and R^{45} are, independently, C_{1-6} alkyl or phenyl;

or a pharmaceutically acceptable salt thereof.

In a further aspect R^3 is heterocyclyl (such as thienyl, isoxazolyl or indolyl, or a naphthyridinyl, an imidazopyridinyl or an isoquinolinyl) optionally substituted by oxo, halogen or C_{1-6} alkyl.

In yet another aspect the present invention provides a compound of formula (Ia) wherein:

T is C(O), C(S), $S(O)_2$ or CH_2;

n is 0, 1, 2, 3, 4 or 5;

m and p are, independently, 0, 1 or 2;

R^{35} is hydrogen, halogen or phenyl (optionally substituted by one or two halogen atoms or by one $C(O)NR^{12'}R^{13'}$, $NR^{9'}C(O)R^{10'}$, $S(O)_2R^{15'}$, $S(O)_2NR^{42}R^{43}$ or $NR^{44}S(O)_2R^{45}$ group);

R^{36} is hydrogen or halogen;

R^3 is C_{1-6} alkyl {optionally substituted by halogen, CO_2R^4 or phthalimide}, C_{3-7} cycloalkyl {optionally substituted by C_{1-4} alkyl or oxo}, aryl or heterocyclyl;

wherein, unless stated otherwise, the foregoing aryl and heterocyclyl moieties are optionally substituted by: halogen, OH, SH, NO_2, oxo, C_{1-6} alkyl (itself optionally substituted by halogen, $OC(O)C_{1-6}$ alkyl, phenyl (itself optionally substituted by halo or C_{1-6} alkyl), naphthyloxy (itself optionally substituted by halo or C_{2-6} alkenyl) or $NR^4C(O)OCH_2$(fluoren-9-yl)), C_{1-6} alkoxy (itself optionally substituted by halogen, CO_2R^4, NR^5R^6 or phenyl (itself optionally substituted by halogen or NO_2)), C_{1-6} alkylthio, nitro, C_{3-7} cycloalkyl, NR^7R^8, $NR^9C(O)R^{10}$, CO_2R^{11}, $C(O)NR^{12}R^{13}$, $C(O)R^{14}$, $S(O)_2R^{15}$, phenyl (itself optionally substituted by NO_2 or C_{1-6} alkoxy (itself optionally substituted by OH or pyridinyl)), phenoxy, SCN, CN, SO_3H (or an alkali metal salt thereof) or methylenedioxy; when aryl is phenyl adjacent substituents may join to form, together with the phenyl ring a dihydrophenanthrene moiety;

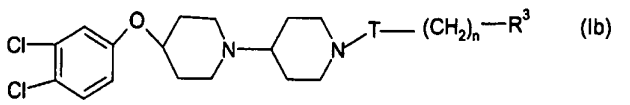
R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, R^{10}, $R^{10'}$, R^{11}, R^{12}, $R^{12'}$, R^{13}, $R^{13'}$, R^{14}, R^{42}, R^{43} and R^{44} are, independently, hydrogen, C_{1-6} alkyl or aryl;

R^{15}, $R^{15'}$ and R^{45} are, independently, C_{1-6} alkyl or aryl;

or a pharmaceutically acceptable salt thereof.

In a further aspect R^{35} and R^{36} are, independently, hydrogen, halogen, (especially fluoro or chloro), C_{1-4} alkyl (especially methyl) or C_{1-4} alkoxy (especially methoxy). In another aspect R^{35} and R^{36} are both chlorine or both fluorine, especially 3,4 disposed on the phenyl ring to which they are attached.

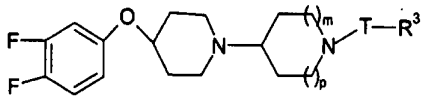
In a further aspect the present invention provides a compound of formula (Ib):



(Ib)

wherein T, n and R^3 are as defined above.

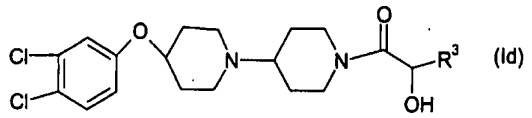
In a still further aspect the present invention provides a compound of formula (Ic):



(Ic)

wherein T, m, p and R^3 are as defined above.

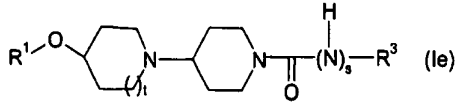
In another aspect the present invention provides a compound of formula (Id):



(Id)

wherein R^3 is as defined above.

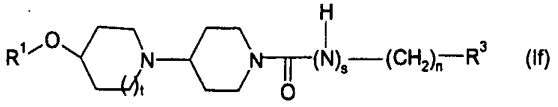
In yet another aspect the present invention provides a compound of formula (Ie):



(Ie)

wherein R^1, t, s and R^3 are as defined above.

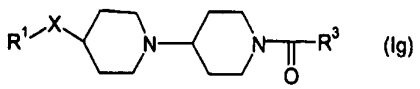
In a further aspect the present invention provides a compound of formula (If):



(If)

wherein R^1, n, t, s and R^3 are as defined above.

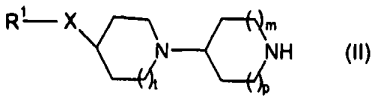
In a still further aspect the present invention provides a compound of formula (Ig):



(Ig)

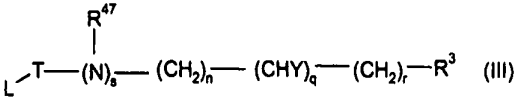
wherein R^1, X and R^3 are as defined above.

A compound of formula (I), wherein s is 0, can be prepared by coupling a compound of formula (II):



(II)

with a compound of formula (III):



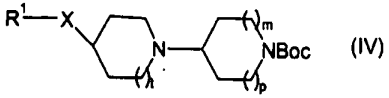
(III)

wherein L is a suitable leaving group, and the variables Y and T are optionally protected during the course of the reaction by standard protecting groups known in the art and deprotected in a separate step or during the reaction work-up. For example:

- when T is carbonyl, L can be OH and the coupling can be carried out in the presence of a coupling agent (such as bromo-tris-pyrrolidino-phosphonium hexafluorophosphate, (known as PYBROP™), oxalyl chloride, thionyl chloride or N,N'-carbonyl diimidazole, or another coupling agent known to a person skilled in the art); or,
- when T is sulphonyl, L can be chloro and the coupling can be carrier out in the presence of a suitable base (such as potassium carbonate) in a suitable solvent (such as acetone).

A compound of formula (I), wherein s is 1, R^{47} is hydrogen and T isCO, can be prepared by reacting a compound of formula (II), wherein m and p are both 1, with an aromatic isocyanate of formula with an isocyanate $O=C=N-(CH_2)_n-(CH_2)_r-R^3$.

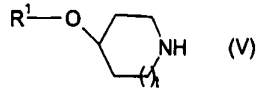
A compound of formula (II) can be prepared by deprotecting a compound of formula (IV):



(IV)

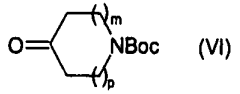
for example using trifluoroacetic acid in a suitable solvent (such as dichloromethane) or using a source of hydrogen chloride in a suitable solvent (such as dioxane).

A compound of formula (IV), wherein X is O, can be prepared by reacting a compound of formula (V):



(V)

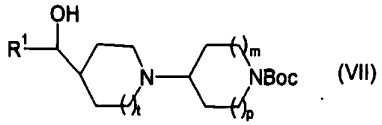
with a compound of formula (VI):



(VI)

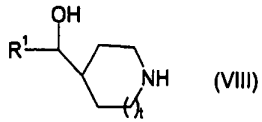
in the presence of $NaBH(OAc)_3$ and acetic acid.

A compound of formula (IV), wherein X is CO or CH_2, can be prepared by oxidising or reducing a compound of formula (VII):



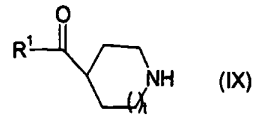
(VII)

A compound of formula (VII) can be prepared by reacting a compound of formula (VIII):



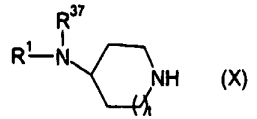
(VIII)

with a compound of formula (VI) in the presence of $NaBH(OAc)_3$ and acetic acid. A compound of formula (VIII) can be prepared by reduction of a compound of formula (IX):



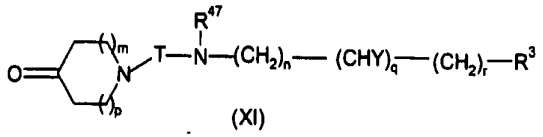
(IX)

A compound of formula (I) wherein X is NR^{37} can be prepared by reacting a compound of formula (X):



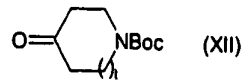
(X)

with a compound of formula (XI):



(XI)

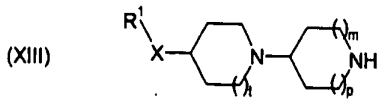
in the presence of $NaBH(OAc)_3$ and acetic acid. A compound of formula (X) can be prepared by reacting NHR^1R^{37} with a compound of formula (XII):



(XII)

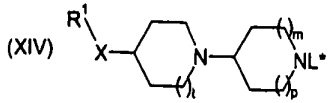
in the presence of $NaBH(OAc)_3$ and acetic acid and then deprotecting the piperidine nitrogen {for example using trifluoroacetic acid in a suitable solvent (such as dichloromethane) or using a source of hydrogen chloride in a suitable solvent (such as dioxane)}.

Alternatively, a compound of formula (I), wherein s, n, q and r are all 0 and T is CO, can be prepared by reacting a compound of formula (XIII):



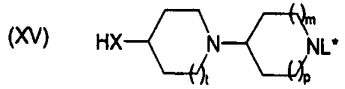
(XIII)

with an acid: R^3CO_2H. A compound of formula (XIII) can be prepared by deprotecting a compound of formula (XIV):



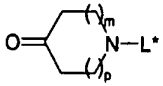
(XIV)

wherein L* is BOC or a benzyl group. A compound of formula (XIV) can be prepared by performing a fluoride displacement reaction on FR^1 in the presence of compound of formula (XV):

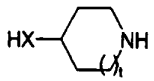


(XV)

A compound of formula (XV) can be prepared by coupling a compound of formula (XVI) with a compound of formula (XVII):

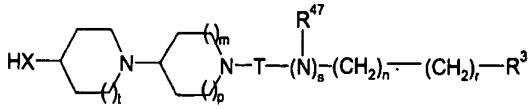


(XVI)



(XVII)

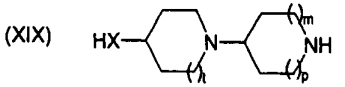
Alternatively, a compound of formula (I) wherein s, n, q and r are all 0 and T is CO, can be prepared by performing a fluoride displacement reaction on FR^1 in the presence of compound of formula (XVIII):



(XVIII)

provided that R^{47} is not hydrogen.

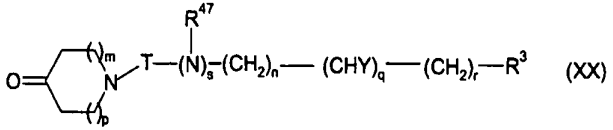
A compound of formula (XVIII) can be prepared by reacting a compound of formula (XIX):



(XIX)

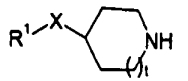
with an appropriate mixed anhydride (such as an anhydride of formula $R^3C(O)OC(O)(C_{1-6}$ alkyl), wherein alkyl is, for example, methyl, ethyl or iso-butyl). A compound of formula (XIX) can be prepared by deprotecting a compound of formula (XV).

Alternatively, a compound of formula (I) can be prepared by reductive ammination of a compound of formula (XX):



(XX)

with an amine of formula (XXI):



(XXI)

under suitable conditions.

Further compounds of formula (I) can be prepared by adaptation of: the routes described above, methods described in the art or the Examples recited below.

Compounds of formula (V), (VI), (IX), (XI), (XII), (XVI) and (XVII) can be prepared by using or adapting methods described in the art.

In another aspect the present invention provides processes for the preparation of compounds of formula (I) (as defined above), (I'), (Ia"), (Ia), (Ia'), (Ib), (Ic), (Id), (Ie), (If) and (Ig).

The intermediates of formula (II), (IV), (XIII), (XIV) and (XVII) defined herein are novel and these, and processes for their preparation, are provided as further features of the invention.

Examples of compounds of formula (Ib) are listed in Table I below.

TABLE I

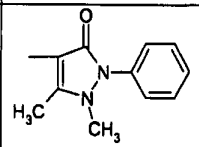
Compound	T	n	R^3	M+H
1	C(O)	0	C_6H_5	433
2	C(O)	0	3,4-Cl_2-C_6H_3	501
3	C(O)	0	2,4-Cl_2-C_6H_3	501
4	C(O)	0	4-CH_3-C_6H_4	447
5	C(O)	0	4-CH_3O-C_6H_4	463
6	C(O)	0	4-CF_3-C_6H_4	501
7	C(O)	0	4-Cl-C_6H_4	467
8	C(O)	0	4-NO_2-C_6H_4	478
9	C(O)	0	3,5-Cl_2-C_6H_3	501
10	C(O)	0	2-F-C_6H_4	451
11	C(O)	0	4-cyclohexyl-C_6H_4	515
12	C(O)	0	4-(n-butoxy)-C_6H_4	505
13	C(O)	0	3-NMe_2-C_6H_4	476
14	C(O)	0	4-(NHC(O)Me)-C_6H_4	490
15	C(O)	0	4-NEt_2-C_6H_4	504
16	C(O)	0	3-CO_2Me-C_6H_4	491

17	C(O)	0	2-C(O)NH_2-C_6H_4	
18	C(O)	0	4-$S(O)_2$Me-C_6H_4	511
19	C(O)	0	2-I-C_6H_4	559
20	C(O)	0	3-phenoxy-C_6H_4	525
21	C(O)	0	2-Me-C_6H_4	447
22	C(O)	0	3-Me-C_6H_4	447
23	C(O)	0	3-I-C_6H_4	559
24	C(O)	0	3-NH_2-6-(NHC_6H_5)-C_6H_3	539
25	C(O)	0	3,5-F_2-C_6H_3	469
26	C(O)	0	3-NO_2-4-(tert-Bu)-C_6H_3	534
27	C(O)	0	3-NO_2-5-(CO_2Me)-C_6H_3	536
28	C(O)	0	2-Me-5-NO_2-C_6H_3	492
29	C(O)	0	3,5-(tert-Bu)$_2$-C_6H_3	545
30	C(O)	0	2-NO_2-5-Me-C_6H_3	492
31	C(O)	0	2-Br-5-MeO-C_6H_3	541
32	C(O)	0	3-MeO-4-(CO_2Me)-C_6H_3	
33	C(O)	0	2-(NHC(O)Me)-5-Br-C_6H_3	568
34	C(O)	0	2-NO_2-5-SCN-C_6H_3	535
35	C(O)	0	3-MeO-4-Me-C_6H_3	477
36	C(O)	0	4-CN-C_6H_4	458
37	C(O)	0	3-CN-C_6H_4	458
38	C(O)	0	2-phenoxy-4-Br-C_6H_3	
39	C(O)	0	2-NH_2-5-I-C_6H_3	574
40	C(O)	0	4-F-C_6H_4	451
41	$S(O)_2$	0	2-CF_3O-C_6H_4	553
42	$S(O)_2$	0	3-NO_2-4-Cl-C_6H_3	548
43	$S(O)_2$	0	Camphor-10-yl (alternatively named 7,7-dimethyl-bicyclo[2.2.1]heptan-2-on-1-yl)	543
44	$S(O)_2$	0	n-Pr	435
45	$S(O)_2$	0	C_6Me_5	539
46	$S(O)_2$	0	4-(n-Pr)-C_6H_4	511
47	$S(O)_2$	0	Naphth-2-yl	519

48	$S(O)_2$	0	2,6-Cl_2-C_6H_3	537
49	$S(O)_2$	0	2,6-F_2-C_6H_3	505
50	$S(O)_2$	0	4-NO_2-C_6H_4	514
51	$S(O)_2$	0	3,4-Cl_2-C_6H_3	537
52	$S(O)_2$	0	2,5-Cl_2-C_6H_3	
53	$S(O)_2$	0	5-(NMe_2)-naphth-1-yl	562
54	$S(O)_2$	0	2,1,3-benzthiadiazol-4-yl	527
55	$S(O)_2$	0	4-Et-C_6H_4	497
56	$S(O)_2$	0	2,5-Cl_2-thien-3-yl	543
57	$S(O)_2$	0	3,4-$(MeO)_2$-C_6H_3	529
58	$S(O)_2$	0	3-CF_3-6-Cl-C_6H_3	571
59	$S(O)_2$	0	5-Cl-thien-2-yl	509
60	$S(O)_2$	0	4-Cl-C_6H_4	503
61	$S(O)_2$	0	4-(iso-Pr)-C_6H_4	511
62	$S(O)_2$	0	2-Cl-4-CF_3-C_6H_3	571
63	$S(O)_2$	0	Benzofuraz-4-yl (other name 2,1,3-benzoxadiazol-4-yl)	511
64	$S(O)_2$	0	3-Me-C_6H_4	483
65	$S(O)_2$	0	2,4-F_2-C_6H_3	505
66	$S(O)_2$	0	2-Me-5-F-C_6H_3	501
67	$S(O)_2$	0	4-CF_3O-C_6H_4	553
68	$S(O)_2$	0	iso-Pr	435
70	$S(O)_2$	0	4-(CO_2H)-C_6H_4	513
71	$S(O)_2$	0	chromen-2-one-6-yl	537
72	$S(O)_2$	0	3,5-Cl_2-C_6H_3	537
73	$S(O)_2$	0	2,3-Cl_2-C_6H_3	537
74	$S(O)_2$	1	4-NO_2-C_6H_4	
75	$S(O)_2$	0	3-CF_3-C_6H_4	537
76	$S(O)_2$	0	4-(tert-Bu)-C_6H_4	525
77	$S(O)_2$	0	3-CO_2H-4-OH-C_6H_3	529
78	$S(O)_2$	0	2-NO_2-C_6H_4	514
79	$S(O)_2$	0	2-F-C_6H_4	487

80	$S(O)_2$	0	3-NO_2-C_6H_4	514
83	$S(O)_2$	0	Naphth-1-yl	519
84	$S(O)_2$	0	2-MeO-5-Cl-C_6H_3	533
85	$S(O)_2$	0	3-F-C_6H_4	487
86	$S(O)_2$	0	3-Cl-4-(NHC(O)Me)-C_6H_3	560
87	$S(O)_2$	1	C_6H_5	483
88	$S(O)_2$	0	2-NO_2-4-MeO-C_6H_3	544
89	$S(O)_2$	0	2-Me-5-NO_2-C_6H_3	528
90	$S(O)_2$	0	3-CO_2H-C_6H_4	513
91	$S(O)_2$	0	2,4,6-Me_3-C_6H_2	511
92	$S(O)_2$	0	Me	
93	$S(O)_2$	0	3,4-Cl_2-C_6H_3	537
94	$S(O)_2$	0	4-MeO-C_6H_4	
95	$S(O)_2$	0	4-NHC(O)Me-C_6H_4	526
96	$S(O)_2$	0	2-CF_3-C_6H_4	537
97	$S(O)_2$	0	$(CH_2)_2CO_2Me$	479
98	$S(O)_2$	0	4-Me-C_6H_4	483
99	$S(O)_2$	0	4-CF_3-C_6H_4	537
100	$S(O)_2$	0	4-CN-C_6H_4	494
101	$S(O)_2$	0	3-NO_2-4-Me-C_6H_3	528
102	$S(O)_2$	0	1H-2-oxo-quinolin-6-yl	
103	$S(O)_2$	0	2-(NHCOMe)-4-methylthiazol-5-yl	547
104	$S(O)_2$	0	Thien-2-yl	475
105	$S(O)_2$	0	Quinolin-8-yl	
106	$S(O)_2$	0	2-OH-3,5-Cl_2-C_6H_2	553
107	$S(O)_2$	0	2-(CO_2Me)-C_6H_4	527
108	$S(O)_2$	0	2,5-$(MeO)_2$-C_6H_3	529
109	$S(O)_2$	0	phenyl	469
110	$S(O)_2$	0	2-Me-4-NO_2-C_6H_3	528
111	$S(O)_2$	0	5-(pyridin-2-yl)thien-2-yl	552
112	$S(O)_2$	0	1,3-Me_2-5-Cl-pyrazol-4-yl	521
113	$S(O)_2$	0	3,5-Me_2-isoxazol-4-yl	488

114	$S(O)_2$	0	2,3,6-Me_3-4-MeO-C_6H	541
115	$S(O)_2$	0	1-Me-imidazol-4-yl	473
116	$S(O)_2$	0	2-MeO-5-Me-C_6H_3	513
117	$S(O)_2$	0	5-(isoxazol-3-yl)thien-2-yl	542
118	$S(O)_2$	0	2-(CO_2Me)thien-3-yl	533
119	$S(O)_2$	0	4-(1,1-dimethylprop-1-yl)-C_6H_4	539
120	$S(O)_2$	0	1-(N-phthalimido)-ethyl	566
121	CH_2	0	4-Me-C_6H_4	433
122	CH_2	0	4-(CO_2H)-C_6H_4	463
123	CH_2	0	2-(CO_2H)-C_6H_4	463
124	CH_2	0	4-(NHC(O)Me)-C_6H_4	476
125	CH_2	0	3-OH-C_6H_4	435
126	CH_2	0	4-MeO-C_6H_4	449
127	CH_2	0	5-Me-fur-2-yl	423
128	CH_2	0	2,5-F_2-C_6H_3	455
129	CH_2	0	5-NO_2-fur-2-yl	
130	CH_2	0	4-NO_2-C_6H_4	
131	CH_2	0	4-iso-Pr-C_6H_4	461
132	CH_2	0	phenyl	419
133	CH_2	0	2-($SO_3^-Na^+$)-C_6H_4	498
134	CH_2	0	4-F-C_6H_4	437
135	CH_2	0	2,6-Cl_2-C_6H_3	487
136	CH_2	0	3,4-Cl_2-C_6H_3	487
137	CH_2	0	2,4-Cl_2-C_6H_3	
138	CH_2	0	4-(OCH_2CO_2H)-C_6H_4	493
139	CH_2	0	Pyrid-2-yl	420
140	CH_2	0	3-methylthien-2-yl	439
141	CH_2	0	3-Cl-C_6H_4	453
142	CH_2	0	5-methylthien-2-yl	439
143	CH_2	0	3-OH-4-MeO-C_6H_3	465
144	CH_2	0	3-NO_2-4-OH-C_6H_3	480
145	CH_2	0	Chromon-3-yl	

146	CH_2	0	1,3-Me_2-5-Cl-pyrazol-4-yl	471
147	CH_2	0	3,4-F_2-C_6H_3	455
148	CH_2	0	4-Cl-pyrazol-3-yl	443
149	C(O)	1	4-$S(O)_2$Me-C_6H_4	
150	CH_2	0	2,6-Cl_2-pyridin-4-yl	
151	CH_2	0	5-(4-NO_2-C_6H_4)-fur-2-yl	530
152	CH_2	0	1-(4-methylbenzyl)-pyrazol-5-yl	
153	CH_2	0	Benzfur-2-yl	459
154	CH_2	0	2-phenylimidazol-4-yl	485
155	CH_2	0	5-ethylthien-2-yl	453
156	CH_2	0	2-Cl-quinolin-3-yl	504
157	CH_2	0	6-methylpyridin-2-yl	434
158	CH_2	0	1-acetylindol-3-yl	500
159	CH_2	0	6-formyl-pyridin-2-yl	448
160	CH_2	0	Quinolin-3-yl	
161	CH_2	0	5-($CH_2OC(O)CH_3$)-fur-2-yl	
162	CH_2	0		529
163	CH_2	0	Pyridin-4-yl	420
164	CH_2	0	3-OH-4-NO_2-C_6H_3	480
165	CH_2	0	3,5-F_2-C_6H_3	455
166	CH_2	0	3-CF_3-C_6H_3	487
167	CH_2	0	2-F-6-Cl-C_6H_3	471
168	CH_2	0	2-(tert-butyl)S-C_6H_4	
169	CH_2	0	4-Et-C_6H_4	447
170	CH_2	0	3-CO_2H-4-OH-C_6H_4	479
171	CH_2	0	3-(OCH_2CO_2H)-C_6H_4	493
172	CH_2	0	2,3-methylenedioxyphenyl	463
173	CH_2	0	Thiazol-2-yl	426
174	CH_2	0	5-ethylfur-2-yl	437

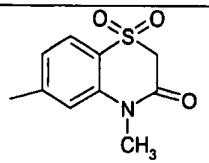
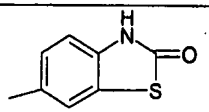
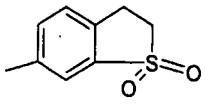
175	CH_2	0	Quinolin-2-yl	470
176	CH_2	0	Quinolin-4-yl	470
177	CH_2	0	4-$CH_2CH(CH_3)_2$-C_6H_4	475
178	CH_2	0	3-MeO-4-OH-5-CO_2H-C_6H_2	509
179	CH_2	0	4-bromopyrazol-3-yl	
180	CH_2	0	2-(OCH_2CO_2H)-3-MeO-C_6H_3	523
181	CH_2	0	4-($O(CH_2)_3N(CH_3)_2$)-C_6H_4	520
182	CH_2	0	3-bromothien-2-yl	503
183	CH_2	0	3-phenoxythien-2-yl	517
184	CH_2	0	5-methylthio-thien-2-yl	471
185	CH_2	0	1-methyl-4-bromopyrazol-3-yl	501
186	CH_2	0	4-I-C_6H_4	
187	CH_2	0	6,7-Me_2-chromon-3-yl	
188	CH_2	0	2-(OCH_2CO_2H)-5-NO_2-C_6H_4	538
189	CH_2	0	2-(2,6-dichlorobenzyloxy)phenyl	593
190	CH_2	0	1-(4-chlorobenzyl)pyrazol-3-yl	533
191	CH_2	0	4-iso-propoxy-C_6H_4	477
192	CH_2	0	1-methylbenzimidazol-2-yl	473
193	CH_2	0	3-Me-C_6H_4	433
194	CH_2	0	Pyridin-3-yl	420
195	CH_2	0	2,4-$(MeO)_2$-pyrimidin-5-yl	
196	CH_2	0	3-Cl-5-CF_3-pyridin-2-yl	522
197	CH_2	0	2,4-Me_2-C_6H_3	447
198	CH_2	0	1-methylindol-3-yl	472
199	CH_2	0	2-methyl-3-(CO_2Et)-fur-5-yl	
200	CH_2	0	1-Me-4-Cl-pyrazol-3-yl	457
201	C(O)	2	phenyl	461
202	C(O)	1	4-Br-C_6H_4	525
203	C(O)	1	4-NH_2-C_6H_4	462
204	C(O)	1	2-Br-C_6H_4	525
205	C(O)	1	4-F-C_6H_4	465
206	C(O)	1	2-CF_3-C_6H_4	

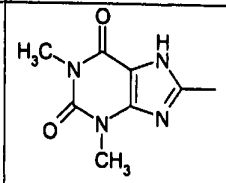
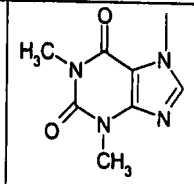
207	C(O)	1	3-Me-C_6H_4	461
208	C(O)	1	2-Me-C_6H_4	461
209	C(O)	1	3-Cl-4-OH-C_6H_3	497
210	C(O)	3	9,10-dihydrophenanthren-2-yl	577
211	C(O)	1	2-NO_2-C_6H_4	492
212	C(O)	1	2-Cl-C_6H_4	481
213	C(O)	1	4-Cl-C_6H_4	481
214	C(O)	1	2-benzyloxy-C_6H_4	553
215	C(O)	2	3,4-$(OH)_2$-C_6H_3	493
216	C(O)	1	4-NO_2-C_6H_4	492
217	C(O)	4	Phenyl	489
218	C(O)	1	3,4-$(MeO)_2$-C_6H_3	507
219	C(O)	1	4-EtO-C_6H_4	491
220	C(O)	1	3-F-4-OH-C_6H_3	481
221	C(O)	3	Phenyl	475
222	C(O)	1	3,4-methylenedioxyphenyl	491
223	C(O)	3	4-MeO-C_6H_4	505
224	C(O)	2	4-OH-C_6H_4	477
225	C(O)	1	4-OH-C_6H_4	463
226	C(O)	1	4-phenyl-C_6H_4	523
227	C(O)	1	3,4-Cl_2-C_6H_3	515
228	C(O)	2	3-OH-C_6H_4	477
229	C(O)	2	4-Me-C_6H_4	475
230	C(O)	3	4-NO_2-C_6H_4	520
231	C(O)	2	3,4-$(MeO)_2$-C_6H_3	521
232	C(O)	3	4-Me-C_6H_4	489
233	C(O)	2	C_6F_5	551
234	C(O)	3	Dibenzothien-4-yl	581
235	C(O)	1	4-Me-C_6H_4	461
236	C(O)	2	4-SH-C_6H_4	
237	C(O)	1	4-CF_3O-C_6H_4	531
238	C(O)	1	4-CH_2Br-C_6H_4	

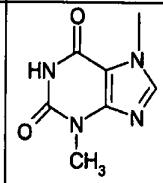
239	C(O)	3	3,4-$(MeO)_2$-C_6H_3	535
240	C(O)	1	4-MeO-C_6H_4	477
241	C(O)	1	4-(NMe_2)-C_6H_4	490
242	C(O)	2	4-MeO-C_6H_4	491
243	C(O)	2	2-MeO-C_6H_4	491
244	C(O)	1	3,4,5-$(MeO)_3$-C_6H_2	537
245	C(O)	2	3,4-methylenedioxyphenyl	505
246	C(O)	2	Dibenzothien-4-yl	
247	C(O)	1	3-NH_2-C_6H_4	462
248	C(O)	1	Naphth-1-yl	497
249	C(O)	1	3-MeO-4-OH-C_6H_3	493
250	C(O)	1	Naphth-2-yl	
251	C(O)	1	3-(1-allyl-6-bromonaphth-2-yloxy)CH_2-C_6H_4	721
252	C(O)	1	4-NO_2-C_6H_4	
253	C(O)	1	3-F-4-MeO-C_6H_3	495
254	C(O)	4	3-Me-C_6H_4	503
255	C(O)	1	3-OH-C_6H_4	463
256	C(O)	1	4-benzyloxy-C_6H_4	553
257	C(O)	1	4-(3-NO_2-C_6H_4)-C_6H_4	568
258	C(O)	1	2,5-$(Me)_2$-C_6H_3	475
259	C(O)	1	4-I-C_6H_4	573
260	C(O)	1	4-(4-(1-Me-2-OH-4-(pyridin-3-yl)-butoxy)-C_6H_4)-C_6H_4	702
261	C(O)	1	3-Br-C_6H_4	525
262	C(O)	2	3-(n-Pr)-C_6H_4	503
263	C(O)	1	4-(4-NO_2-$C_6H_4CH_2O$)-C_6H_4	598
264	C(O)	1	2,5-$(OH)_2$-C_6H_3	
265	C(O)	1	2-Me-3-NO_2-C_6H_3	506
266	C(O)	1	4-($CH_2NHCO_2CH_2$(fluoren-9-yl))-C_6H_4	
267	C(O)	1	3-OH-4-MeO-C_6H_4	493
268	C(O)	1	3-F-C_6H_4	465
269	C(O)	1	2-F-C_6H_4	465

270	C(O)	1	3,5-$(MeO)_2$-C_6H_3	507
271	C(O)	1	3-Cl-C_6H_4	481
272	C(O)	1	Phenyl	447
273	C(O)	1	3,5-Me_2-C_6H_3	475
274	C(O)	2	3-MeO-C_6H_4	491
275	C(O)	1	2,4-F_2-C_6H_3	483
276	C(O)	1	2-MeO-C_6H_4	477
277	C(O)	1	3,4-F_2-C_6H_3	483
278	C(O)	1	3,5-F_2-C_6H_3	483
279	C(O)	5	phenyl	503
280	$S(O)_2$	0	5-(pyridin-2-yl)-thien-2-yl	
281	C(O)	0	3-$S(O)_2Me$-C_6H_4	511
282	C(O)	0	3-MeO-4-NH_2-C_6H_3	
283	C(O)	0	3-MeO-4-F-C_6H_3	481
284	C(O)	0	Benzthiazol-6-yl	490
285	C(O)	0	3-MeO-C_6H_4	477
286	C(O)	0	3-$C_6H_5S(O)$-C_6H_4	557
287	C(O)	0	4-$S(O)_2Me$-C_6H_4	511
288	C(O)	0	2,4-Cl_2-C_6H_3	501
289	C(O)	0	4-NO_2-C_6H_4	478
290	C(O)	0	3-CN-C_6H_4	458
291	C(O)	0	4-MeO-C_6H_4	463
292	C(O)	0	4-CN-C_6H_4	458
293	C(O)	0	2-$S(O)_2Me$-C_6H_4	511
294	C(O)	0	2-Cl-4-$S(O)_2Me$-C_6H_3	545
295	C(O)	0	3-($C_6H_5S(O)_2CH_2$)-4-NO_2-C_6H_3	632
296	C(O)	0	2-($C_6H_5S(O)_2CH_2$)-C_6H_4	
297	C(O)	0	Benzo[1,2,3]thiadiazol-5-yl	491
298	C(O)	0	4-EtS-C_6H_4	493
299	C(O)	0	3-CF_3S-C_6H_4	533
300	C(O)	0	4-CF_3S-C_6H_4	533
301	C(O)	0	3-$CH_3C(O)NH$-C_6H_4	490

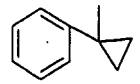
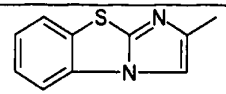
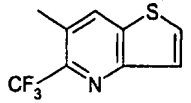
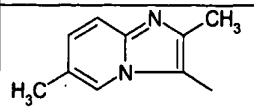
302	C(O)	0	3-CH_3-4-NH_2-C_6H_3	462
303	C(O)	0	Indol-7-yl	472
304	C(O)	0	3-CH_3CH_2O-4-CH_3O-C_6H_3	507
305	C(O)	0	4-(2,5-dihydropyrrol-1-yl)-C_6H_4	500
306	C(O)	1	3-Br-pyridin-5-yl	526
307	C(O)	1	1-methyl-imidazol-4-yl	451
308	C(O)	1	5-OH-indol-3-yl	502
309	C(O)	1	Thiophen-3-yl	453
310	C(O)	0	3-$CH_3CH_2S(O)_2$-C_6H_4	525
311	C(O)	0	3-$CH_3(CH_2)_2S(O)_2$-C_6H_4	539
312	C(O)	0	3-$(CH_3)_2CHCH_2S(O)_2$-C_6H_4	553
313	C(O)	0	3,4-$(CH_3S(O)_2)_2$-C_6H_3	589
314	C(O)	0	3-CH_3CH_2O-4-NH_2-C_6H_3	492
315	C(O)	1	Pyridin-4-yl	448
316	C(O)	0	2-$CH_3S(O)_2CH_2$-C_6H_4	525
317	C(O)	0	2-NH_2-C_6H_4	448
318	C(O)	0	1-acetyl-indol-3-yl	
319	C(O)	0	Indol-3-yl	
320	C(O)	0	3-$NH_2(CH_2)_2O$-C_6H_4	
321	C(O)	0	3-$CH_3NHS(O)_2$-C_6H_4	
322	C(O)	0	3-$NH_2S(O)_2$-C_6H_4	
323	C(O)	0	3-$CH_3O(CH_2)_2O$-C_6H_4	
324	C(O)	0	3-$(CH_3)_3COC(O)NH(CH_2)_2O$-$C_6H_4$	
325	C(O)	0	1,2,3-benzothiadiazol-6-yl	
326	C(O)	0	3-$HOC(O)CH_2O$-C_6H_4	
327	C(O)	0	2-$CH_3S(O)_2$-3-CN-thiophen-5-yl	542
328	C(O)	0	3-$CH_3S(O)_2$-4-NH_2-C_6H_3	526
329	C(O)	0	2-$CH_3S(O)_2$-3-$NH_2C(O)$-thiophen-5-yl	560
330	C(O)	0	3-CF_3O-C_6H_4	501
331	C(O)	0	2-$(CH_3)_2CHS(O)_2$-3-NH_2-thiophen-4-yl	560
332	C(O)	0	2-$CH_3S(O)_2$-thiophen-5-yl	517

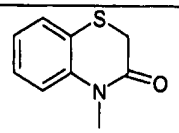
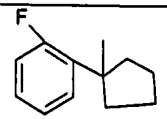
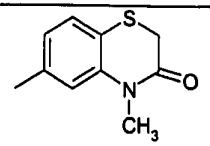
333	C(O)	0	3-CH_3-5-(4-CH_3-1,2,3-thiadiazol-5-yl)-isoxazol-4-yl	536
334	C(O)	0	3-Cl-5-CF_3-pyridin-2-yl	536
335	C(O)	1	4-CF_3O-C_6H_4	531
336	C(O)	0	1H-benzotriazol-5-yl	474
337	C(O)	0	4-$CH_3S(O)_2CH_2$-C_6H_4	525
338	C(O)	0	3-$CH_3S(O)_2CH_2$-C_6H_4	525
339	C(O)	0	2-CN-C_6H_4	458
340	C(O)	0	Quinolin-6-yl	484
341	C(O)	0	Quinoxalin-6-yl	485
342	C(O)	0	3-NH_2-4-$CH_3S(O)_2$-thiophen-2-yl	532
343	C(O)	0		566
344	C(O)	0		
345	C(O)	0	3-CF_3O-C_6H_4	517
346	C(O)	0	2,5-$(CH_3O)_2$-C_6H_3	493
347	C(O)	0	1-$(CH_3)_2CH$-benzotriazol-5-yl	
348	C(O)	0		
349	C(O)	0	3-$HO(CH_2)_2S(O)_2$-C_6H_4	
350	C(O)	0	2-$HO(CH_2)_2S(O)_2$-C_6H_4	
351	C(O)	0	3-cyclopropyl$CH_2S(O)_2$-C_6H_4	
352	C(O)	0	2-$CH_3S(O)_2NH$-C_6H_4	526
353	C(O)	0	$(CF_3)(MeO)(C_6H_5)C$	545
354	C(O)	0	$(C_6H_5)_2CH$	523

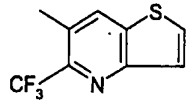
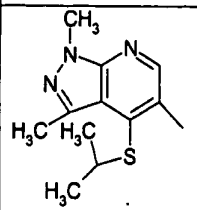
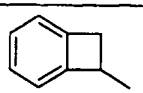
355	C(O)	0	(4-Cl-C_6H_4)$(CH_3)_2C$	509
356	C(O)	0	(C_6H_5)(cyclohexyl)CH	529
357	C(O)	0	(4-F-C_6H_4)(CH_3)CH	479
358	C(O)	1	3,4-methylenedioxy-C_6H_4	491
359	C(O)	0	(C_6H_5)(cyclopentyl)CH	515
360	C(O)	0	$((CH_3)(CH_3CH_2)$CH)(C_6H_5)CH	503
361	C(O)	0	1-phenyl-cyclopentyl	501
362	C(O)	0	1-(4-Cl-C_6H_4)cyclopentyl	535
363	C(O)	0	1-phenyl-cyclopropyl	473
364	C(O)	0	1-phenyl-cyclohexyl	515
365	C(O)	0	(C_6H_5)(cyclohexyl)C(OH)	545
366	C(O)	0	$((CH_3)_2$CH)(C_6H_5)CH	489
367	C(O)	1	pyrid-3-yl	448
368	C(O)	1	pyrid-2-yl	448
369	C(O)	1	5-Br-pyrid-3-yl	526
370	C(O)	1	2,4-$(MeO)_2$-C_6H_3	507
371	C(O)	1	4-benzyloxy-phenyl	553
372	C(O)	1	3-benzyloxy-phenyl	553
373	C(O)	1		549
374	C(O)	0	2-EtO-C_6H_4	491
375	C(O)	0		549
376	C(O)	1	4-n-butoxyphenyl	519
377	C(O)	1	indol-1-yl	486
378	C(O)	1	2-NO_2-phenyl	492

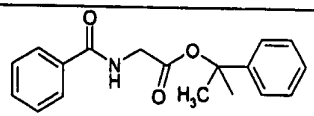
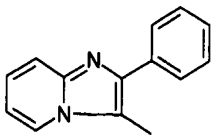
379	C(O)	1	thien-2-yl	453
380	C(O)	1	3-Cl-4-OH-phenyl	497
381	C(O)	1	2-Br-phenyl	525
382	C(O)	1	3-Br-phenyl	525
383	C(O)	1	3,5-F_2-phenyl	483
384	C(O)	1	3-aminophenyl	462
385	C(O)	1	3,4-$(OH)_2$-phenyl	479
386	C(O)	1	2,5-$(MeO)_2$-phenyl	507
387	C(O)	1	4-Me-phenyl	461
388	C(O)	0	5-(4-Cl-C_6H_4)-tetrazol-2-yl	549
389	C(O)	1	4-$MeS(O)_2$-phenyl	525
390	C(O)	1	4-F-phenyl	465
391	C(O)	1	5-Cl-benzo[b]thiophen-3-yl	537
392	C(O)	1	4-CF_3O-phenyl	531
393	C(O)	1	3-Me-5-Cl-benzo[b]thiophen-2-yl	551
394	C(O)	1	2-nitrophenyl	492
395	C(O)	1	4-Cl-5-Me-3-NO_2-pyrazol-1-yl	530
396	C(O)	1	2-CF_3-benzimidazol-1-yl	555
397	C(O)	1	2-EtS-benzimidazol-1-yl	547
398	C(O)	1	2-Me-4-(thien-2-yl)-thiazol-5-yl	550
399	C(O)	1	4-Br-3,5-Me_2-pyrazol-1-yl	543
400	C(O)	1	5-Me-3,4-$(NO_2)_2$-pyrazol-1-yl	541
401	C(O)	1	4-(3-methyl-butoxy)-phenyl	533
402	C(O)	1	2-tert-butylthio-phenyl	535
403	C(O)	1	4-Cl-3,5-Me_2-pyrazol-1-yl	499
404	C(O)	1		535
405	C(O)	1	2,4-$(NO_2)_2$-imidazol-1-yl	527
406	C(O)	1	3,5-Me_2-pyrazol-1-yl	465

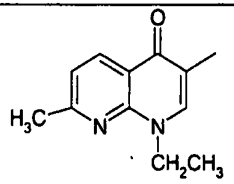
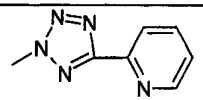
407	C(O)	1	4-n-hexyl-phenyl	531
408	C(O)	0	2-NH_2-pyrid-5-yl	449
409	C(O)	0	Pyrid-2-yl	434
410	C(O)	0	2-EtS-pyrid-3-yl	494
411	C(O)	0	2-OH-quinolin-4-yl	500
412	C(O)	0	2-OH-pyrid-5-yl	450
413	C(O)	0	2,6-$(MeO)_2$-pyrid-3-yl	494
414	C(O)	0	2-(imidazol-1-yl)-pyrid-5-yl	500
415	C(O)	0	2-CO_2CH_3-pyrid-3-yl	492
416	C(O)	0	2-Me-pyrid-5-yl	448
417	C(O)	0	Quinolin-2-yl	484
418	C(O)	0	6-Me-pyrid-2-yl	448
419	C(O)	0	2-OH-6-Me-pyrid-3-yl	464
420	C(O)	0	8-OH-quinolin-2-yl	500
421	C(O)	1	3-F-phenyl	465
422	C(O)	0	Imidazo[1,2-a]pyrid-2-yl	473
423	C(O)	0	2-methyl-[1,8]naphthyridin-3-yl	499
424	C(O)	0	[1,6]naphthyridin-2-yl	485
425	C(O)	0	2-methyl-[1,6]naphthyridin-3-yl	499
426	C(O)	0	1-methyl-1H-pyrid-2-one-5-yl	464
427	C(O)	0	Quinolin-4-yl	484
428	C(O)	0	Quinolin-6-yl	484
429	C(O)	0	3-$(CH_3(CH_2)_2S(O)_2)$-C_6H_4	539
430	C(O)	0	5-((pyrid-2-yl)SCH_2)fur-2-yl	546
431	C(O)	0	2-Me-3-OH-quinolin-4-yl	514
432	C(O)	0	(pyrid-2-yl)CH=CH	460
433	C(O)	0	(2-EtS-pyrid-5-yl)CH=CH	520
434	C(O)	0	1-(5-CF_3-pyrid-2-yl)-piperidin-4-yl	585
435	C(O)	0	2,7-Me_2-imidazo[1,2-a]pyrid-3-yl	501
436	C(O)	0	(5-CF_3-pyrid-2-yl)$SO_2CH(CH_3)$	594
437	C(O)	1	3-(pyrid-2-yl)pyrazol-1-yl	514
438	C(O)	0	3-NH_2-4-CH_3O-C_6H_3	478

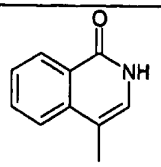
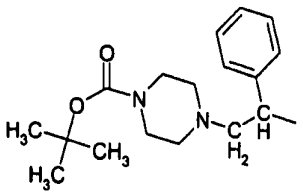
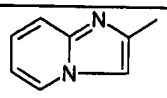
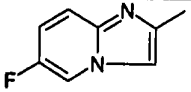
439	C(O)	0	2,5-$(CH_3O)_2$-C_6H_3	493
440	C(O)	0	3-F-4-CH_3-C_6H_3	465
441	C(O)	0	3-phenyl-5-CH_3-isoxazol-4-yl	514
442	C(O)	0	1-phenyl-5-CH_3-pyrazol-4-yl	513
443	C(O)	0	3-CF_3O-C_6H_4	517
444	C(O)	0	2-CH_3O-5-Cl-C_6H_3	497
445	C(O)	0	2-CH_3-3-F-C_6H_3	465
446	C(O)	0	2-(2-phenyl-thiazol-4-yl)phenyl	592
447	C(O)	0	3,4-methylenedioxyphenyl	477
448	C(O)	0	5-phenyl-oxazol-4-yl	500
449	C(O)	0	1H-indazol-3-yl	473
450	C(O)	0	1-CH_3-indol-3-yl	486
451	C(O)	0	1-iso-propyl-benztriazol-5-yl	516
452	C(O)	0		473
453	C(O)	0	2-CH_3-5-F-C_6H_3	465
454	C(O)	0	3-CF_3O-4-NH_2-C_6H_3	532
455	C(O)	0	3-CH_3-5-CF_3-isoxazol-4-yl	506
456	C(O)	0	(1,2,4-triazol-1-yl)$C(CH_3)_2$	466
457	C(O)	0	2-phenyl-thiazol-4-yl	516
458	C(O)	0	2-CH_3-4-CF_3-thiazol-5-yl	522
459	C(O)	0		529
460	C(O)	0		558
461	C(O)	0	3-F-4-CF_3-C_6H_3	519
462	C(O)	0		501

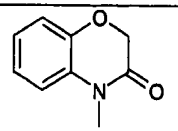
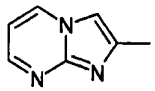
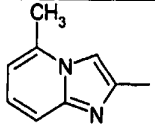
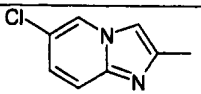
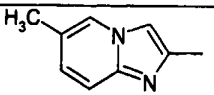
463	C(O)	0	2-CH_3-benzimidazol-5-yl	487
464	C(O)	1		534
465	C(O)	0	3-iso-propoxy-4-CH_3O-C_6H_3	521
466	C(O)	0		519
467	C(O)	0		534
468	C(O)	0	2-CH_3O-5-F-C_6H_3	481
469	C(O)	0	3-CH_3CH_2O-C_6H_4	
470	C(O)	0	2-($C_6H_5S(O)CH_2$)-C_6H_4	
471	C(O)	0	1H-indol-3-yl	472
472	$S(O)_2$	1	2-NO_2-C_6H_4	528
473	$S(O)_2$	0	2-CN-C_6H_4	494
474	C(O)	0	3-$CH_3S(O)_2$-C_6H_4	511
475	C(O)	0	3-$S(O)_2NHCH_3$-C_6H_4	526
476	C(O)	0	Benzo[1,2,3]thiadiazol-6-yl	491
477	C(O)	0	3-$CH_3O(CH_2)_2O$-C_6H_4	507
478	C(O)	0	3,4-$(CH_3S(O)_2)_2$-C_6H_3	589
479	C(O)	0	3-CH_3O-C_6H_4	463
480	C(O)	0	3-CN-C_6H_4	458
481	C(O)	0	4-F-C_6H_4	451
482	C(O)	0	3-CH_3O-4-F-C_6H_3	481
483	C(O)	0	3H-benzothiazol-2-one-6-yl	506
484	C(O)	0	2-$CH_3S(O)_2$-thien-5-yl	517
485	C(O)	0	3-CH_3-4-NH_2-C_6H_3	462
486	C(O)	0	Benzothiazol-6-yl	490

487	C(O)	0	1H-5-$CH_3S(O)_2$-indol-2-yl	550
488	C(O)	0	1H-5-CH_3O-indol-2-yl	502
489	C(O)	0	1H-indol-4-yl	472
490	C(O)	0	1H-Benzimidazol-5-yl	473
491	C(O)	0	3,4-methylenedioxyphenyl	477
492	C(O)	0	1H-5-Cl-indol-2-yl	506
493	C(O)	0	1H-5-OH-indol-2-yl	488
494	C(O)	0		558
495	C(O)	0	3,4-difluoromethylenedioxyphenyl	513
496	C(O)	0	2-(pyrazol-1-yl)-pyridin-5-yl	500
497	C(O)	0	4-CF_3-pyridin-3-yl	502
498	C(O)	0		576
499	C(O)	0		459
500	C(O)	0	3-n-propoxy-pyridin-2-yl	492
501	C(O)	1	2-(2,4-F_2-C_6H_3)thiazol-4-yl	566
502	C(O)	0	1H-indol-2-yl	472
503	C(O)	1	2-phenyl-5-CH_3-thiazol-4-yl	544
504	C(O)	0	2-$S(O)_2NH_2$-4-Cl-C_6H_3	546
505	C(O)	0	2-CN-C_6H_4	458
506	C(O)	0	1H-indol-7-yl	472
507	C(O)	0	1H-5-F-indol-2-yl	490
508	C(O)	0	1H-pyrazol-4-yl	423
509	C(O)	0	1-CH_3-pyrrol-2-yl	436

511	C(O)	0	3-(pyrrol-1-yl)-4-CN-thien-2-yl	529
512	C(O)	0	3-CH_3O-4-NH_2-C_6H_3	478
513	C(O)C(O)	0	1H-indol-3-yl	500
514	C(O)	0	4-(pyrrol-1-yl)phenyl	498
515	C(O)	0	1-CH_3-indol-2-yl	486
516	C(O)	1	1H-indol-3-yl	486
517	C(O)	1	1H-5-CH_3O-indol-3-yl	516
518	C(O)	0	2-(pyridin-2-yl)-thien-5-yl	516
519	C(O)	0	1H-5-F-indol-2-yl	490
520	C(O)	1	3-CH_3-benzo[b]thiophen-2-yl	517
521	C(O)	1	3,5-$(CH_3)_2$-4-NO_2-pyrazol-1-yl	510
522	C(O)	0	2-CF_3-[1,6]-naphthyridin-3-yl	553
523	C(O)	0	2-(1-CH_3-5-CF_3-pyrazol-3-yl)-thien-5-yl	587
524	C(O)	0		638
525	C(O)	1	3-Cl-C_6H_4	481
526	C(O)	1	5-CH_3-3-NO_2-pyrazol-1-yl	496
527	C(O)	1	2-CN-C_6H_4	472
528	C(O)	0	Quinoxalin-2-yl	485
529	C(O)	0	Pyrazin-2-yl	435
530	C(O)	0		549
531	C(O)	0	1-tert-butyl-3-CH_3-pyrazol-5-yl	493
532	C(O)	0	2-SH-pyridin-3-yl	466
533	C(O)	0	Quinolin-3-yl	484

534	C(O)	0		543
535	C(O)	0	2-ethoxy-phenyl	477
536	C(O)	1	4-NO_2-imidazol-1-yl	482
537	C(O)	0	4-CH_3O-quinolin-2-yl	514
538	C(O)	0	2-$SCH_2CH{=}CH_2$-pyridin-3-yl	506
539	C(O)	0	1-iso-propyl-benztriazol-5-yl	516
540	C(O)	0	[1,8]-naphthyridin-2-yl	485
541	C(O)	1	2-CH_3-4-phenyl-thiazol-5-yl	544
542	C(O)	0	1-CH_3-indol-2-yl	486
543	C(O)	0	2-phenoxy-pyridin-5-yl-CH=CH	552
544	C(O)	1	3,4-Cl_2-C_6H_3	515
545	C(O)	0	2-$S(O)_2CH_3$-3-CN-6-CH_3-pyridin-4-yl	551
546	C(O)	0	3H-Benzothiazol-2-one-6-yl	506
547	C(O)	0	2-CH_3O-pyridin-3-yl	464
548	C(O)	0	Isoquinolin-1-yl	484
549	C(O)	1	4-OH-C_6H_4	463
550	C(O)	0	Quinolin-8-yl	484
551	C(O)	0	2-CN-C_6H_4	458
552	C(O)	0	2-CF_3-[1,8]-naphthyridin-3-yl	553
553	C(O)	0	2-CO_2CH_3-pyridin-6-yl	492
554	C(O)	0	Isoquinolin-3-yl	484
555	C(O)	0	3-$CH_2S(O)_2CH_3$-C_6H_4	525
556	C(O)	0	2-ethoxy-pyridin-3-yl	478
557	C(O)	1		516
558	C(O)	0	2-CH_3O-pyridin-5-yl	464
559	C(O)	0	Indan-1-one-3-yl	487

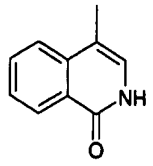
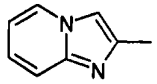
560	C(O)	1	3-NO_2-[1,2,4]-triazol-1-yl	483
561	C(O)	0	1-$(CH_3)_2CH$-benzotriazol-5-yl	516
562	C(O)	1	1H-2-CH_3-indol-3-yl	500
563	C(O)	0	3,5-$(CH_3)_2$-isoxazol-4-yl	452
564	C(O)	0	1,5-$(CH_3)_2$-pyrazol-4-yl	451
565	C(O)	0	Quinoxalin-6-yl	485
566	C(O)	1	3-NO_2-[1,2,4]triazol-1-yl	483
567	C(O)	0	1H-indol-3-yl-CH=CH	498
568	C(O)	1	4-(pyridin-2-yl)-pyrimidin-2-yl-S	558
569	C(O)	0	3-$S(O)_2NH_2$-C_6H_4	512
570	C(O)	1	1H-5-OH-indol-3-yl	502
571	C(O)	0	4-$CH_2S(O)_2CH_3$-C_6H_4	525
572	C(O)	0		500
573	C(O)	0	Isoxazol-5-yl	424
574	C(O)	1	1-CH_3-4-NO_2-pyrazol-5-yl	496
575	C(O)	0		645
576	C(O)	0	3-ethoxy-4-amino-phenyl	492
577	C(O)	1	1,4-$(CH_3)_2$-3-CO_2H-pyrrol-2-yl	508
578	C(O)	0		473
579	C(O)	0		491

580	C(O)	0	2-OH-quinolin-4-yl	500
582	C(O)	0	3-amino-phenyl	448
583	C(O)	0	3-$NHS(O)_2CH_3$-C_6H_4	526
584	C(O)	0	3-$C(CH_3)_3OC(O)NH(CH_2)_2O$-$C_6H_4$	592
585	C(O)	0	3-HO_2CCH_2O-C_6H_4	507
586	C(O)	0	3-$H_2N(CH_2)_2O$-C_6H_4	492
587	C(O)	0	2-$NHS(O)_2CH_3$-C_6H_4	526
588	C(O)	0	2-$S(O)_2CH_2$cyclopropyl-C_6H_4	551
589	C(O)	0	3-$S(O)_2N(CH_3)_2$-C_6H_4	540
590	C(O)	0	3-NO_2-5-$S(O)_2CH_3$-C_6H_3	556
591	C(O)	0	3-NH_2-5-$S(O)_2CH_3$-C_6H_3	526
592	C(O)	0	1-$S(O)_2CH_3$-indol-3-yl	
593	C(O)	0	3-CN-5-$S(O)_2CH_3$-C_6H_3	536
594	C(O)	0	1H-5-$S(O)_2CH_3$-indol-3-yl	550
595	C(O)	0	CH(Phenyl)(CH_2piperazin-1-yl)	545
596	C(O)	1		518
597	C(O)	0	3-$S(O)_2NH_2$-4-Cl-C_6H_3	546
598	C(O)	0		474
599	C(O)	0		487
600	C(O)	0		507
601	C(O)	0		487

602	C(O)	0	2-NO_2-5-$S(O)_2CH_3$-C_6H_3	
603	C(O)	0	2-NH_2-5-$S(O)_2CH_3$-C_6H_3	

Examples of compounds of formula (Ic) are listed in Table II below.

TABLE II

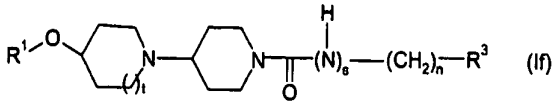
Compound	m	p	T	R^3
1	1	1	C(O)	3-MeO-4-NH_2-C_6H_3
2	0	2	C(O)	3-MeO-4-NH_2-C_6H_3
3	1	1	$S(O)_2$	5-(pyridin-2-yl)-thien-2-yl
4	0	1	C(O)	3-MeO-4-NH_2-C_6H_3
5	1	1	C(O)	3H-benzthiazol-2-one-6-yl
6	1	1	C(O)	
7	1	1	C(O)	[1,8]naphthyridin-2-yl
8	1	1	C(O)	

Examples of compounds of formula (Id) are listed in Table III below.

TABLE III

Compound	R^3
1	4-F-C_6H_4
2	Phenyl
3	3,4-F_2-C_6H_3

Examples of compounds of formula (If) are listed in Table IV below.



(If)

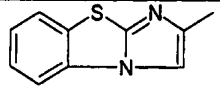
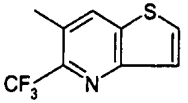
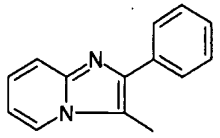
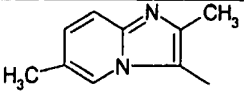
TABLE IV

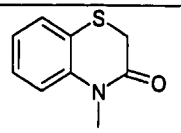
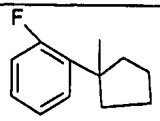
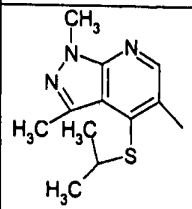
Compound	R^1	t	s	n	R^3
1	2-CH_3-4-Cl-C_6H_3	1	0	0	3-$CH_3S(O)_2$-C_6H_4
2	3-Cl-4-F-C_6H_3	1	0	0	3-$CH_3S(O)_2$-C_6H_4
3	3-F-4-Cl-C_6H_3	1	0	0	3-$CH_3S(O)_2$-C_6H_4
4	3-CH_3O-4-Cl-C_6H_3	1	0	0	3-$CH_3S(O)_2$-C_6H_4
5	2-CH_3O-4-F-C_6H_3	1	0	0	3-$CH_3S(O)_2$-C_6H_4
6	4-CH_3O-C_6H_4	1	0	0	3-$CH_3S(O)_2$-C_6H_4
7	4-CH_3O-C_6H_4	0	0	0	3-$CH_3S(O)_2$-C_6H_4
8	4-Cl-C_6H_4	0	0	0	3-$CH_3S(O)_2$-C_6H_4
9	3,4-Cl_2-C_6H_3	0	0	0	3-$CH_3S(O)_2$-C_6H_4
10	4-CN-C_6H_4	0	0	0	3-$CH_3S(O)_2$-C_6H_4
11	3,4-F_2-C_6H_3	0	0	0	3-$CH_3S(O)_2$-C_6H_4
12	4-F-C_6H_4	0	0	0	3-$CH_3S(O)_2$-C_6H_4
13	4-$CH_3C(O)NH$-C_6H_4	1	0	0	3-$CH_3S(O)_2$-C_6H_4
14	4-CH_3-C_6H_4	1	0	0	3-$CH_3S(O)_2$-C_6H_4
15	3-CH_3-4-Cl-C_6H_3	1	0	0	3-$CH_3S(O)_2$-C_6H_4
16	4-Cl-C_6H_4	1	0	0	3-$CH_3S(O)_2$-C_6H_4
17	4-F-C_6H_4	1	0	0	3-$CH_3S(O)_2$-C_6H_4
18	2,4-Cl_2-C_6H_3	1	0	0	3-$CH_3S(O)_2$-C_6H_4
19	2-Cl-4-F-C_6H_3	1	0	0	3-$CH_3S(O)_2$-C_6H_4
20	2,4-F_2-C_6H_3	1	0	0	3-$CH_3S(O)_2$-C_6H_4
21	2-F-4-Cl-C_6H_3	1	0	0	3-$CH_3S(O)_2$-C_6H_4
22	2-CH_3-4-F-C_6H_3	1	0	0	3-$CH_3S(O)_2$-C_6H_4
23	2-CH_3-4-Cl-C_6H_3	1	0	0	3-CH_3O-4-NH_2-C_6H_3
24	3-F-4-Cl-C_6H_3	1	0	0	3-CH_3O-4-NH_2-C_6H_3
25	2-CH_3O-4-Cl-C_6H_3	1	0	0	3-CH_3O-4-NH_2-C_6H_3
26	2-CH_3O-4-F-C_6H_3	1	0	0	3-CH_3O-4-NH_2-C_6H_3
27	4-CH_3O-C_6H_4	1	0	0	3-CH_3O-4-NH_2-C_6H_3
28	3-Cl-4-F-C_6H_3	1	0	0	3-CH_3O-4-NH_2-C_6H_3
29	4-CH_3-C_6H_4	1	0	0	3-CH_3O-4-NH_2-C_6H_3
30	3-CH_3-4-Cl-C_6H_3	1	0	0	3-CH_3O-4-NH_2-C_6H_3

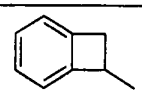
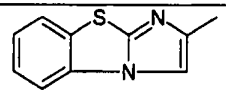
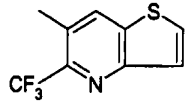
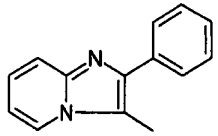
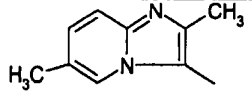
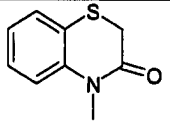
31	4-Cl-C_6H_4	1	0	0	3-CH_3O-4-NH_2-C_6H_3
32	4-F-C_6H_4	1	0	0	3-CH_3O-4-NH_2-C_6H_3
33	2,4-Cl_2-C_6H_3	1	0	0	3-CH_3O-4-NH_2-C_6H_3
34	2-Cl-4-F-C_6H_3	1	0	0	3-CH_3O-4-NH_2-C_6H_3
35	2,4-F_2-C_6H_3	1	0	0	3-CH_3O-4-NH_2-C_6H_3
36	2-F-4-Cl-C_6H_3	1	0	0	3-CH_3O-4-NH_2-C_6H_3
37	2-CH_3-4-F-C_6H_3	1	0	0	3-CH_3O-4-NH_2-C_6H_3
38	2-CH_3-4-Cl-C_6H_3	1	0	0	1,2,3-benzthiadiazol-5-yl
39	3-F-4-Cl-C_6H_3	1	0	0	1,2,3-benzthiadiazol-5-yl
40	2-CH_3O-4-Cl-C_6H_3	1	0	0	1,2,3-benzthiadiazol-5-yl
41	2-CH_3O-4-F-C_6H_3	1	0	0	1,2,3-benzthiadiazol-5-yl
42	4-CH_3O-C_6H_4	1	0	0	1,2,3-benzthiadiazol-5-yl
43	3-Cl-4-F-C_6H_3	1	0	0	1,2,3-benzthiadiazol-5-yl
44	4-CH_3-C_6H_4	1	0	0	1,2,3-benzthiadiazol-5-yl
45	3-Cl-4-CH_3-C_6H_3	1	0	0	1,2,3-benzthiadiazol-5-yl
46	4-Cl-C_6H_4	1	0	0	1,2,3-benzthiadiazol-5-yl
47	4-F-C_6H_4	1	0	0	1,2,3-benzthiadiazol-5-yl
48	2,4-Cl_2-C_6H_3	1	0	0	1,2,3-benzthiadiazol-5-yl
49	2-Cl-4-F-C_6H_3	1	0	0	1,2,3-benzthiadiazol-5-yl
50	2,4-F_2-C_6H_3	1	0	0	1,2,3-benzthiadiazol-5-yl
51	2-F-4-Cl-C_6H_3	1	0	0	1,2,3-benzthiadiazol-5-yl
52	2-CH_3-4-F-C_6H_3	1	0	0	1,2,3-benzthiadiazol-5-yl
53	3,4-Cl_2-C_6H_3	1	1	0	3-CN-C_6H_4
54	3,4-Cl_2-C_6H_3	1	1	0	3-$CH_3S(O)_2$-C_6H_4
55	2-CH_3-4-Cl-C_6H_3	1	0	0	2-$CH_3S(O)_2$-C_6H_4
56	3-Cl-4-F-C_6H_3	1	0	0	2-$CH_3S(O)_2$-C_6H_4
57	3-F-4-Cl-C_6H_3	1	0	0	2-$CH_3S(O)_2$-C_6H_4
58	3-CH_3O-4-Cl-C_6H_3	1	0	0	2-$CH_3S(O)_2$-C_6H_4
59	2-CH_3O-4-F-C_6H_3	1	0	0	2-$CH_3S(O)_2$-C_6H_4
60	4-CH_3O-C_6H_4	1	0	0	2-$CH_3S(O)_2$-C_6H_4
61	4-$CH_3C(O)NH$-C_6H_4	1	0	0	2-$CH_3S(O)_2$-C_6H_4
62	4-CH_3-C_6H_4	1	0	0	2-$CH_3S(O)_2$-C_6H_4

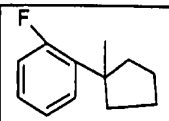
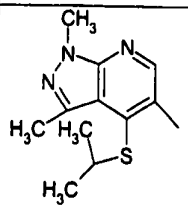
63	3-CH_3-4-Cl-C_6H_3	1	0	0	2-$CH_3S(O)_2$-C_6H_4
64	4-Cl-C_6H_4	1	0	0	2-$CH_3S(O)_2$-C_6H_4
65	4-F-C_6H_4	1	0	0	2-$CH_3S(O)_2$-C_6H_4
66	2,4-Cl_2-C_6H_3	1	0	0	2-$CH_3S(O)_2$-C_6H_4
67	2-Cl-4-F-C_6H_3	1	0	0	2-$CH_3S(O)_2$-C_6H_4
68	2,4-F_2-C_6H_3	1	0	0	2-$CH_3S(O)_2$-C_6H_4
69	2-F-4-Cl-C_6H_3	1	0	0	2-$CH_3S(O)_2$-C_6H_4
70	2-CH_3-4-F-C_6H_3	1	0	0	2-$CH_3S(O)_2$-C_6H_4
71	2-CH_3-4-Cl-C_6H_3	1	0	0	2-$CH_3S(O)_2$-thiophen-5-yl
72	3-Cl-4-F-C_6H_3	1	0	0	2-$CH_3S(O)_2$-thiophen-5-yl
73	3-F-4-Cl-C_6H_3	1	0	0	2-$CH_3S(O)_2$-thiophen-5-yl
74	3-CH_3O-4-Cl-C_6H_3	1	0	0	2-$CH_3S(O)_2$-thiophen-5-yl
75	2-CH_3O-4-F-C_6H_3	1	0	0	2-$CH_3S(O)_2$-thiophen-5-yl
76	4-CH_3O-C_6H_4	1	0	0	2-$CH_3S(O)_2$-thiophen-5-yl
77	4-$CH_3C(O)NH$-C_6H_4	1	0	0	2-$CH_3S(O)_2$-thiophen-5-yl
78	4-CH_3-C_6H_4	1	0	0	2-$CH_3S(O)_2$-thiophen-5-yl
79	3-CH_3-4-Cl-C_6H_3	1	0	0	2-$CH_3S(O)_2$-thiophen-5-yl
80	4-Cl-C_6H_4	1	0	0	2-$CH_3S(O)_2$-thiophen-5-yl
81	4-F-C_6H_4	1	0	0	2-$CH_3S(O)_2$-thiophen-5-yl
82	2,4-Cl_2-C_6H_3	1	0	0	2-$CH_3S(O)_2$-thiophen-5-yl
83	2-Cl-4-F-C_6H_3	1	0	0	2-$CH_3S(O)_2$-thiophen-5-yl
84	2,4-F_2-C_6H_3	1	0	0	2-$CH_3S(O)_2$-thiophen-5-yl
85	2-F-4-Cl-C_6H_3	1	0	0	2-$CH_3S(O)_2$-thiophen-5-yl
86	2-CH_3-4-F-C_6H_3	1	0	0	2-$CH_3S(O)_2$-thiophen-5-yl
87	3-Cl-4-CH_3-C_6H_3	1	0	0	3-$CH_3S(O)_2$-C_6H_4
88	3-Cl-4-CH_3-C_6H_3	1	0	0	3-CH_3O-4-NH_2-C_6H_3
89	3-CH_3-4-Cl-C_6H_3	1	0	0	1,2,3-benzthiadiazol-5-yl
90	3-Cl-4-CH_3-C_6H_3	1	0	0	2-$CH_3S(O)_2$-C_6H_4
91	3-Cl-4-CH_3-C_6H_3	1	0	0	2-$CH_3S(O)_2$-thiophen-5-yl
92	2-CH_3-4-Cl-C_6H_3	1	0	0	Quinolin-6-yl
93	2-CH_3-4-Cl-C_6H_3	1	0	0	3-($CH_3O(CH_2)_2O$)-C_6H_4
94	2-CH_3-4-Cl-C_6H_3	1	0	0	3,4-($CH_3S(O)_2$)$_2$-C_6H_3

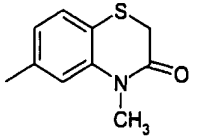
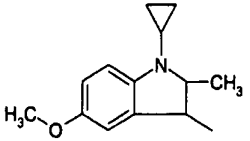
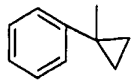
95	2-CH_3-4-Cl-C_6H_3	1	0	0	3-CH_3O-C_6H_4
96	2-CH_3-4-Cl-C_6H_3	1	0	0	3-CN-C_6H_4
97	2-CH_3-4-Cl-C_6H_3	1	0	0	4-F-C_6H_4
98	2-CH_3-4-Cl-C_6H_3	1	0	0	Indol-7-yl
99	2-CH_3-4-Cl-C_6H_3	1	0	0	5-$CH_3S(O)_2$-indol-2-yl
100	2-CH_3-4-Cl-C_6H_3	1	0	0	Benzimidazol-5-yl
101	2-CH_3-4-Cl-C_6H_3	1	0	0	3,4-methylenedioxy-C_6H_3
102	2-CH_3-4-Cl-C_6H_3	1	0	0	5-F-indol-2-yl
103	2-CH_3-4-Cl-C_6H_3	1	0	0	5-CF_3-thieno[3,2-b]pyridin-6-yl
104	2-CH_3-4-Cl-C_6H_3	1	0	0	2-(pyrazol-1-yl)-pyridin-5-yl
105	3-CH_3-4-Cl-C_6H_3	1	0	0	Quinolin-6-yl
106	3-CH_3-4-Cl-C_6H_3	1	0	0	2-CN-C_6H_4
107	3-CH_3-4-Cl-C_6H_3	1	0	0	3-($CH_3O(CH_2)_2O$)-C_6H_4
108	3-CH_3-4-Cl-C_6H_3	1	0	0	3,4-($CH_3S(O)_2$)$_2$-C_6H_3
109	3-CH_3-4-Cl-C_6H_3	1	0	0	3-CH_3O-C_6H_4
110	3-CH_3-4-Cl-C_6H_3	1	0	0	3-CN-C_6H_4
111	3-CH_3-4-Cl-C_6H_3	1	0	0	4-F-C_6H_4
112	3-CH_3-4-Cl-C_6H_3	1	0	0	5-$CH_3S(O)_2$-thien-2-yl
113	3-CH_3-4-Cl-C_6H_3	1	0	0	Indol-7-yl
114	3-CH_3-4-Cl-C_6H_3	1	0	0	5-$CH_3S(O)_2$-indol-2-yl
115	3-CH_3-4-Cl-C_6H_3	1	0	0	3-EtO-4-NH_2-C_6H_3
116	3-CH_3-4-Cl-C_6H_3	1	0	0	5-CH_3O-indol-2-yl
117	3-CH_3-4-Cl-C_6H_3	1	0	0	3,4-methylenedioxy-C_6H_3
118	3-CH_3-4-Cl-C_6H_3	1	0	0	5-F-indol-2-yl
119	3-CH_3-4-Cl-C_6H_3	1	0	0	5-CF_3-thieno[3,2-b]pyridin-6-yl
120	3-CH_3-4-Cl-C_6H_3	1	0	0	2-(pyrazol-1-yl)-pyridin-5-yl
121	2-CH_3-4-Cl-C_6H_3	1	0	0	2-NH_2-4-MeO-C_6H_3
122	2-CH_3-4-Cl-C_6H_3	1	0	0	Pyrazin-2-yl
123	2-CH_3-4-Cl-C_6H_3	1	0	0	3-phenyl-5-Me-isoxazol-4-yl
124	2-CH_3-4-Cl-C_6H_3	1	0	0	3-CF_3O-C_6H_4
125	2-CH_3-4-Cl-C_6H_3	1	0	0	2-MeO-5-Cl-C_6H_3
126	2-CH_3-4-Cl-C_6H_3	1	0	0	2-Me-3-F-C_6H_3

127	2-CH_3-4-Cl-C_6H_3	1	0	0	2-EtO-C_6H_4
128	2-CH_3-4-Cl-C_6H_3	1	0	0	5-phenyl-oxazol-4-yl
129	2-CH_3-4-Cl-C_6H_3	1	0	0	5-F-1H-indol-2-yl
130	2-CH_3-4-Cl-C_6H_3	1	0	0	2H-isoquinolin-1-one-4-yl
131	2-CH_3-4-Cl-C_6H_3	1	0	0	3H-benzothiazol-2-one-6-yl
132	2-CH_3-4-Cl-C_6H_3	1	0	0	Bicyclo[4.2.0]octa-1,3,5-trien-7-yl
133	2-CH_3-4-Cl-C_6H_3	1	0	0	1-iso-propylbenztriazol-5-yl
134	2-CH_3-4-Cl-C_6H_3	1	0	0	1-phenylcyclopropyl
135	2-CH_3-4-Cl-C_6H_3	1	0	0	3-$NH_2S(O)_2$-4-Cl-C_6H_3
136	2-CH_3-4-Cl-C_6H_3	1	0	0	3-CF_3O-4-NH_2-C_6H_3
137	2-CH_3-4-Cl-C_6H_3	1	0	0	3-(pyrrol-1-yl)-4-CN-thien-2-yl
138	2-CH_3-4-Cl-C_6H_3	1	0	0	2-($CH_3O(CH_2)_2O$)-5-NH_2-C_6H_3
139	2-CH_3-4-Cl-C_6H_3	1	0	0	1-(1-CH_3-5-CF_3-pyrazol-3-yl)-thien-5-yl
140	2-CH_3-4-Cl-C_6H_3	1	0	0	(1,2,4-triazol-1-yl)C(CH_3)$_2$
141	2-CH_3-4-Cl-C_6H_3	1	0	0	2-phenyl-thiazol-4-yl
142	2-CH_3-4-Cl-C_6H_3	1	0	0	2-CH_3-4-CF_3-thiazol-5-yl
143	2-CH_3-4-Cl-C_6H_3	1	0	0	[1,8]-naphthyridin-2-yl
144	2-CH_3-4-Cl-C_6H_3	1	0	0	
145	2-CH_3-4-Cl-C_6H_3	1	0	0	
146	2-CH_3-4-Cl-C_6H_3	1	0	0	3-F-4-CF_3-C_6H_3
147	2-CH_3-4-Cl-C_6H_3	1	0	0	
148	2-CH_3-4-Cl-C_6H_3	1	0	0	

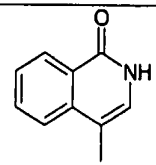
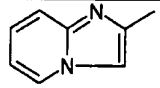
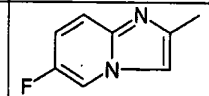
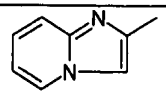
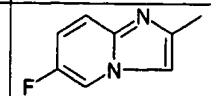
149	2-CH_3-4-Cl-C_6H_3	1	0	0	2-CH_3-benzimidazol-5-yl
150	2-CH_3-4-Cl-C_6H_3	1	0	1	
151	2-CH_3-4-Cl-C_6H_3	1	0	0	
152	2-CH_3-4-Cl-C_6H_3	1	0	0	1,5-dimethyl-pyrazol-3-yl
153	2-CH_3-4-Cl-C_6H_3	1	0	0	2-CH_3O-5-F-C_6H_3
154	3-CH_3-4-Cl-C_6H_3	1	0	0	3-NH_2-4-CH_3O-C_6H_3
155	3-CH_3-4-Cl-C_6H_3	1	0	0	2,5-$(CH_3O)_2$-C_6H_3
156	3-CH_3-4-Cl-C_6H_3	1	0	0	3-F-4-CH_3-C_6H_3
157	3-CH_3-4-Cl-C_6H_3	1	0	0	Pyrazin-2-yl
158	3-CH_3-4-Cl-C_6H_3	1	0	0	3-phenyl-5-CH_3-isoxazol-4-yl
159	3-CH_3-4-Cl-C_6H_3	1	0	0	1-phenyl-5-CH_3-pyrazol-4-yl
160	3-CH_3-4-Cl-C_6H_3	1	0	0	3-CF_3O-C_6H_4
161	3-CH_3-4-Cl-C_6H_3	1	0	0	2-CH_3O-5-Cl-C_6H_3
162	3-CH_3-4-Cl-C_6H_3	1	0	0	2-CH_3-3-F-C_6H_3
163	3-CH_3-4-Cl-C_6H_3	1	0	0	2-CH_3CH_2O-C_6H_4
164	3-CH_3-4-Cl-C_6H_3	1	0	0	2-(2-phenyl-thiazol-4-yl)-phenyl
165	3-CH_3-4-Cl-C_6H_3	1	0	0	
166	3-CH_3-4-Cl-C_6H_3	1	0	0	3,4-methylenedioxyphenyl
167	3-CH_3-4-Cl-C_6H_3	1	0	0	5-phenyl-oxazol-4-yl
168	3-CH_3-4-Cl-C_6H_3	1	0	0	Quinoxalin-2-yl
169	3-CH_3-4-Cl-C_6H_3	1	0	0	1H-Pyrazol-4-yl
170	3-CH_3-4-Cl-C_6H_3	1	0	0	1-CH_3-indol-3-yl

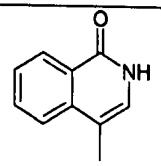
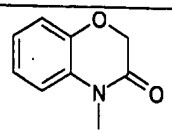
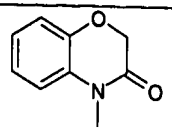
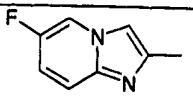
171	3-CH_3-4-Cl-C_6H_3	1	0	0	
172	3-CH_3-4-Cl-C_6H_3	1	0	0	1-iso-propyl-benztriazol-5-yl
173	3-CH_3-4-Cl-C_6H_3	1	0	0	3-n-propoxy-pyridin-2-yl
174	3-CH_3-4-Cl-C_6H_3	1	0	0	2-CH_3-5-F-C_6H_3
175	3-CH_3-4-Cl-C_6H_3	1	0	1	(2-$S(O)_2NHCH_3$-C_6H_4)S
176	3-CH_3-4-Cl-C_6H_3	1	0	0	3-CH_3-5-CF_3-isoxazol-4-yl
177	3-CH_3-4-Cl-C_6H_3	1	0	1	2-(2,4-F_2-C_6H_3)thiazol-4-yl
178	3-CH_3-4-Cl-C_6H_3	1	0	0	2-$(CH_3O(CH_2)_2O)$-5-NH_2-C_6H_3
179	3-CH_3-4-Cl-C_6H_3	1	0	0	2-phenyl-thiazol-4-yl
180	3-CH_3-4-Cl-C_6H_3	1	0	0	
181	3-CH_3-4-Cl-C_6H_3	1	0	0	
182	3-CH_3-4-Cl-C_6H_3	1	0	0	3-F-4-CF_3-C_6H_3
183	3-CH_3-4-Cl-C_6H_3	1	0	0	
184	3-CH_3-4-Cl-C_6H_3	1	0	0	
185	3-CH_3-4-Cl-C_6H_3	1	0	0	3-iso-propoxy-C_6H_4
186	3-CH_3-4-Cl-C_6H_3	1	0	0	2-CH_3-benzimidazol-5-yl
187	3-CH_3-4-Cl-C_6H_3	1	0	1	
188	3-CH_3-4-Cl-C_6H_3	1	0	0	1-CH_3-indol-3-yl

189	3-CH_3-4-Cl-C_6H_3	1	0	0	
190	3-CH_3-4-Cl-C_6H_3	1	0	0	1-tert-butyl-3-CH_3-pyrazol-5-yl
191	3-CH_3-4-Cl-C_6H_3	1	0	0	
192	3-CH_3-4-Cl-C_6H_3	1	0	0	2-CH_3O-5-F-C_6H_3
193	3-CH_3-4-Cl-C_6H_3	1	0	0	3-NH_2-4-CH_3O-C_6H_3
194	3-CH_3-4-Cl-C_6H_3	1	0	0	2,5-$(CH_3O)_2$-C_6H_3
195	2-CH_3-4-Cl-C_6H_3	1	0	0	2-CN-C_6H_4
196	2-CH_3-4-Cl-C_6H_3	1	0	0	2-CH_3O-4-F-C_6H_3
197	3-CH_3-4-Cl-C_6H_3	1	0	0	1-CH_3-pyrrol-2-yl
198	2-CH_3-4-Cl-C_6H_3	1	0	0	3-$S(O)_2CH_3$-4-NH_2-C_6H_3
199	2-CH_3-4-Cl-C_6H_3	1	0	0	1H-5-F-indol-2-yl
200	3-CH_3-4-Cl-C_6H_3	1	0	0	1H-5-CH_3O-indol-3-yl
201	2-CH_3-4-Cl-C_6H_3	1	0	0	3-F-4-CH_3-C_6H_3
202	2-CH_3-4-Cl-C_6H_3	1	0	0	1-phenyl-5-CH_3-pyrazol-4-yl
203	2-CH_3-4-Cl-C_6H_3	1	0	0	2-(2-phenyl-thiazol-4-yl)-phenyl
204	3-CH_3-4-Cl-C_6H_3	1	0	0	1H-5-F-indol-2-yl
205	3-CH_3-4-Cl-C_6H_3	1	0	0	3-CF_3O-4-NH_2-C_6H_3
206	3-CH_3-4-Cl-C_6H_3	1	0	0	3-iso-propoxy-4-CH_3O-C_6H_3
207	2-CH_3-4-Cl-C_6H_3	1	0	0	1H-5-CH_3O-indol-2-yl
208	2-CH_3-4-Cl-C_6H_3	1	0	0	1H-indol-4-yl
209	2-CH_3-4-Cl-C_6H_3	1	0	0	4-CF_3-pyridin-3-yl
210	2-CH_3-4-Cl-C_6H_3	1	0	0	

211	2-CH_3-4-Cl-C_6H_3	1	0	0	1-CH_3-indol-3-yl
212	2-CH_3-4-Cl-C_6H_3	1	0	0	3-iso-propoxy-4-CH_3O-C_6H_3
213	3-CH_3-4-Cl-C_6H_3	1	0	1	1H-indol-3-yl
214	2-CH_3-4-Cl-C_6H_3	1	0	0	
215	2-CH_3-4-Cl-C_6H_3	1	0	0	1-CH_3-indol-2-yl
216	3-CH_3-4-Cl-C_6H_3	1	0	0	3-$S(O)_2NH_2$-4-Cl-C_6H_3
217	3-CH_3-4-Cl-C_6H_3	1	0	0	
218	3-CH_3-4-Cl-C_6H_3	1	0	0	3-(pyrrol-1-yl)-3-CN-thien-2-yl
219	2-CH_3-4-Cl-C_6H_3	1	0	0	4-(pyrrol-1-yl)phenyl
220	3-CH_3-4-Cl-C_6H_3	1	0	0	1H-indazol-3-yl
221	2-CH_3-4-Cl-C_6H_3	1	0	0	3-CH_3O-NH_2-C_6H_3
222	2-CH_3-4-Cl-C_6H_3	1	0	0	1-CH_3-indol-2-yl
223	3-CH_3-4-Cl-C_6H_3	1	0	0	
224	2-CH_3-4-Cl-C_6H_3	1	0	0	4-$S(O)_2CH_3$-C_6H_4
225	3-CH_3-4-Cl-C_6H_3	1	0	0	2-(1-CH_3-5-CF_3-pyrazol-3-yl)-thien-5-yl
226	2-CH_3-4-Cl-C_6H_3	1	0	0	2-CH_3-5-F-C_6H_3
227	2-CH_3-4-Cl-C_6H_3	1	0	0	4-$CH_2S(O)_2CH_3$-C_6H_4
228	2-CH_3-4-Cl-C_6H_3	1	0	0	Quinoxalin-2-yl
229	2-CH_3-4-Cl-C_6H_3	1	0	0	1H-5-Cl-indol-2-yl
230	3-CH_3-4-Cl-C_6H_3	1	0	0	3-$CH_2S(O)_2CH_3$-C_6H_4
231	2-CH_3-4-Cl-C_6H_3	1	0	1	2-(2,4-F_2-C_6H_3)thiazol-4-yl
232	2-CH_3-4-Cl-C_6H_3	1	0	0	3-$S(O)_2NH_2$-C_6H_4
233	2-CH_3-4-Cl-C_6H_3	1	0	1	1H-indol-3-yl

234	3-CH_3-4-Cl-C_6H_3	1	0	0	4-$S(O)_2CH_3$-C_6H_4
235	3-CH_3-4-Cl-C_6H_3	1	0	0	1-CH_3-indol-2-yl
236	2-CH_3-4-Cl-C_6H_3	1	0	0	3-CH_3-5-CF_3-isoxazol-4-yl
237	3-CH_3-4-Cl-C_6H_3	1	0	0	1-CH_3-indol-2-yl
238	4-$S(O)_2CH_3$-C_6H_4	1	0	0	3,4-Cl_2-C_6H_3
239	2-CH_3-4-Cl-C_6H_3	1	0	0	1-CH_3-indol-3-yl
240	3-CH_3-4-Cl-C_6H_3	1	0	0	[1,8]-naphthyridin-2-yl
241	2-CH_3-4-Cl-C_6H_3	1	0	0	3-$S(O)_2CH_3$-C_6H_4
242	3-CH_3-4-Cl-C_6H_3	1	0	0	3-OH-C_6H_4
243	3-CH_3-4-Cl-C_6H_3	1	0	0	3H-Benzthiazol-2-one-6-yl
244	2-CH_3-4-Cl-C_6H_3	1	0	0	3-n-propoxy-pyridin-2-yl
245	2-CH_3-4-Cl-C_6H_3	1	0	0	3H-Benzthiazol-2-one-6-yl
246	2-CH_3-4-Cl-C_6H_3	1	0	0	Isoxazol-5-yl
247	2-CH_3-4-Cl-C_6H_3	1	0	0	2,5-$(CH_3O)_2$-C_6H_3
248	2-CH_3-4-Cl-C_6H_3	1	0	0	1H-pyrazol-4-yl
249	3-CH_3-4-Cl-C_6H_3	1	0	0	Benzothiazol-6-yl
250	2-CH_3-4-Cl-C_6H_3	1	0	0	3,5-$(CH_3)_2$-isoxazol-4-yl
251	3-CH_3-4-Cl-C_6H_3	1	0	0	4-CF_3-pyridin-3-yl
252	3-CH_3-4-Cl-C_6H_3	1	0	0	1H-indol-4-yl
253	3-CH_3-4-Cl-C_6H_3	1	0	0	1,5-$(CH_3)_2$-pyrazol-3-yl
254	2-CH_3-4-Cl-C_6H_3	1	0	0	1H-indazol-3-yl
255	3-CH_3-4-Cl-C_6H_3	1	0	0	3-$S(O)_2NH_2$-C_6H_4
256	2-CH_3-4-Cl-C_6H_3	1	0	1	4-$S(O)_2CH_3$-C_6H_4
257	2-CH_3-4-Cl-C_6H_3	1	0	0	Benzthiazol-6-yl
258	2-CH_3-4-Cl-C_6H_3	1	0	0	1H-5-OH-indol-2-yl
259	2-CH_3-4-Cl-C_6H_3	1	0	0	3-$CH_2S(O)_2CH_3$-C_6H_4
260	2-CH_3-4-Cl-C_6H_3	1	0	0	3,4-methylenedioxyphenyl
261	2-CH_3-4-Cl-C_6H_3	1	0	0	1-CH_3-pyrrol-2-yl
262	2-CH_3-4-Cl-C_6H_3	1	0	0	3-CH_3-4-NH_2-C_6H_3
263	3-CH_3-4-Cl-C_6H_3	1	0	0	Isoxazol-5-yl
264	2-CH_3-4-Cl-C_6H_3	1	0	0	3-OH-C_6H_4
265	2-CH_3-4-Cl-C_6H_3	1	0	0	1H-5-OH-indol-3-yl

266	3-CH_3-4-Cl-C_6H_3	1	0	0	
267	2-CH_3-4-Cl-C_6H_3	1	0	0	
268	2-CH_3-4-Cl-C_6H_3	1	0	0	
269	3-CH_3-4-Cl-C_6H_3	1	0	0	
270	3-CH_3-4-Cl-C_6H_3	1	0	0	
271	2-CH_3O-4-Cl-C_6H_3	1	0	0	3-$CH_3S(O)_2$-C_6H_4
272	2,6-$(CH_3)_2$-4-Cl-C_6H_2	1	0	0	3-$CH_3S(O)_2$-C_6H_4
273	2,3-Cl_2-C_6H_3	1	0	0	3-$CH_3S(O)_2$-C_6H_4
274	2,5-Cl_2-C_6H_3	1	0	0	3-$CH_3S(O)_2$-C_6H_4
275	2-Cl-4-CH_3-C_6H_3	1	0	0	3-$CH_3S(O)_2$-C_6H_4
276	2-Cl-5-CH_3-C_6H_3	1	0	0	3-$CH_3S(O)_2$-C_6H_4
277	2-CH_3-4-$C(O)CH_3$-C_6H_3	1	0	0	3-$CH_3S(O)_2$-C_6H_4
278	2-(morpholin-4-yl)-C_6H_4	1	0	0	3-$CH_3S(O)_2$-C_6H_4
279	3-CH_3CH_2-4-Cl-C_6H_3	1	0	0	3-$CH_3S(O)_2$-C_6H_4
280	Naphth-7-yl	1	0	0	3-$CH_3S(O)_2$-C_6H_4
281	2-tert-butyl-C_6H_4	1	0	0	3-$CH_3S(O)_2$-C_6H_4
282	Indan-5-yl	1	0	0	3-$CH_3S(O)_2$-C_6H_4
283	2-cyclohexyl-4-Cl-C_6H_3	1	0	0	3-$CH_3S(O)_2$-C_6H_4
284	2-$C(O)NH_2$-4-Cl-C_6H_3	1	0	0	3-$CH_3S(O)_2$-C_6H_4

285	2-isoxazol-5-yl-4-Cl-C_6H_3	1	0	0	3-$CH_3S(O)_2$-C_6H_4
286	2-CH_3-5-Cl-C_6H_3	1	0	0	3-$CH_3S(O)_2$-C_6H_4
287	phenyl	1	0	0	3-$CH_3S(O)_2$-C_6H_4
288	2,4-Cl_2-6-CH_3-C_6H_2	1	0	0	3-$CH_3S(O)_2$-C_6H_4
289	3-Cl-4-CH_3-C_6H_3	1	0	0	3-$CH_3S(O)_2$-C_6H_4
290	2-CN-4-CH_3-C_6H_3	1	0	0	3-$CH_3S(O)_2$-C_6H_4
291	2-CN-4-CF_3-C_6H_3	1	0	0	3-$CH_3S(O)_2$-C_6H_4
292	2-CH_3-pyridin-6-yl	1	0	0	3-$CH_3S(O)_2$-C_6H_4
293	Pyrimidin-2-yl	1	0	0	3-$CH_3S(O)_2$-C_6H_4
294	2-Cl-4-F-C_6H_3	1	0	0	2-Cl-4-$CH_3S(O)_2$-C_6H_3
295	2-CH_3-4-Cl-C_6H_3	1	0	0	2-$CH_3S(O)_2$-C_6H_4
296	2-CH_3-4-Cl-C_6H_3	1	0	0	2-Cl-4-$CH_3S(O)_2$-C_6H_3
297	2-CH_3-4-Cl-C_6H_3	1	0	0	3-$S(O)_2NH_2$-4-Cl-C_6H_3
298	2-CH_3-4-Cl-C_6H_3	1	0	0	
299	2,4-Cl_2-3-CH_3-C_6H_2	1	0	0	3-$S(O)_2CH_3$-C_6H_4
300	2-ethyl-4-F-C_6H_3	1	0	0	3-$S(O)_2CH_3$-C_6H_4
301	2-CH_3-4-Cl-C_6H_3	1	0	0	1H-5-$S(O)_2CH_3$-indol-2-yl
302	2-CH_3-4-Cl-C_6H_3	1	0	1	
303	3-CH_3-4-Cl-C_6H_3	1	0	1	
304	2,4-Cl_2-3-CH_3-C_6H_2	1	0	0	

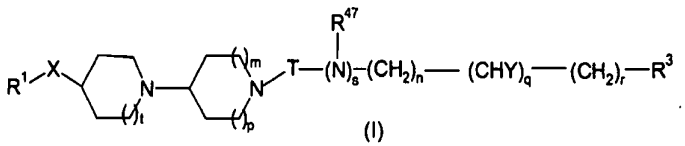
305	2,4-Cl_2-3-CH_3-C_6H_2	1	0	0	2-(pyrazol-1-yl)-pyridin-5-yl
306	2,4-Cl_2-3-CH_3-C_6H_2	1	0	0	2-$S(O)_2CH_3$-thien-5-yl
307	2,4-Cl_2-3-CH_3-C_6H_2	1	0	0	4-$S(O)_2CH_3$-C_6H_4
308	5-CF_3-pyridin-2-yl	1	0	0	3-$S(O)_2CH_3$-C_6H_4
309	3,4-Cl_2-C_6H_3	1	1	0	phenyl
310	3,4-Cl_2-C_6H_3	1	1	0	4-OCH_3-C_6H_4
311	3,4-Cl_2-C_6H_3	1	1	0	4-F-C_6H_4
312	3,4-Cl_2-C_6H_3	1	1	0	3-SCH_3-C_6H_4
313	3,4-Cl_2-C_6H_3	1	1	1	phenyl
314	3,4-Cl_2-C_6H_3	1	1	1	4-OCH_3-C_6H_4
315	3,4-Cl_2-C_6H_3	1	1	1	4-F-C_6H_4

Examples of compounds of formula (Ig) are listed in Table V below.

Table V

	R^1	X	R^3
1	3,4-Cl_2-C_6H_3	CH_2	3-$S(O)_2CH_3$-C_6H_4
2	3,4-Cl_2-C_6H_3	NH	3-$S(O)_2CH_3$-C_6H_4
3	3,4-Cl_2-C_6H_3	C(O)	3-$S(O)_2CH_3$-C_6H_4
4	3,4-Cl_2-C_6H_3	$S(O)_2$	4-$S(O)_2CH_3$-C_6H_4
5	3,4-Cl_2-C_6H_3	$S(O)_2$	C_6H_5

The compounds of formula (I):



(I)

wherein:

q, s and t are, independently, 0 or 1;

n and r are, independently, 0, 1, 2, 3, 4 or 5;

m and p are, independently, 0, 1 or 2;

X is CH_2, C(O), O, S, S(O), $S(O)_2$ or NR^{37};

Y is NHR^2 or OH;

T is C(O), C(S), $S(O)_2$ or CH_2;

R^1 is hydrogen, C_{1-6} alkyl, aryl or heterocyclyl;

R^2 and R^{47} are, independently, hydrogen, C_{1-6} alkyl, aryl(C_{1-4})alkyl or CO(C_{1-6} alkyl);

R^3 is C_{1-6} alkyl {optionally substituted by halogen, CO_2R^4 or phthalimide}, $CR^{3a}R^{3b}R^{3c}$, C_{2-4} alkenyl {optionally substituted by aryl or heterocyclyl}, C_{3-7} cycloalkyl {optionally substituted by C_{1-4} alkyl, aryl or oxo}, C_{3-7} cycloalkenyl {optionally substituted by oxo, C_{1-6} alkyl or aryl}, aryl, heterocyclyl, thioaryl or thioheterocyclyl;

R^{3a} is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy or C_{3-7} cycloalkyl; R^{3b} is aryl, heterocyclyl, $S(O)_2$aryl or $S(O)_2$heterocyclyl; and R^{3c} is C_{1-6} alkyl, C_{1-4} haloalkyl, hydroxy, heterocyclyl(C_{1-4} alkyl) or aryl;

wherein, unless stated otherwise, the foregoing aryl and heterocyclyl moieties are optionally substituted by: halogen, OH, SH, NO_2, oxo, C_{1-6} alkyl {itself optionally substituted by halogen, $OC(O)C_{1-6}$ alkyl, $S(O)_2R^{48}$, phenyl (itself optionally substituted by halogen (such as one or two chlorine or fluorine atoms), C_{1-6} alkyl, $S(O)_2R^{38}$ or $C(O)NR^{39}R^{40}$), naphthyloxy (itself optionally substituted by halo or C_{2-6} alkenyl), C_{3-10} cycloalkyl (itself optionally substituted by C_{1-4} alkyl or oxo) or $NR^{41}C(O)OCH_2$(fluoren-9-yl)}, $NR^{41}C(O)OCH_2$(fluoren-9-yl), C_{1-6} alkoxy {itself optionally substituted by halogen, C_{1-6} alkoxy, $NHCO_2(C_{1-6}$ alkyl), CO_2R^4, NR^5R^6 or phenyl (itself optionally substituted by halogen or NO_2)}, C_{1-6} alkylthio, C_{1-6} haloalkylthio, C_{3-10} cycloalkyl, NR^7R^8, $NR^9C(O)R^{10}$, CO_2R^{11}, $C(O)NR^{12}R^{13}$, $C(O)R^{14}$, $S(O)_dR^{15}$, $S(O)_2NR^{42}R^{43}$, $NR^{44}S(O)_2R^{45}$, phenyl {itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy (itself optionally substituted by halogen, OH or pyridinyl), phenyl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy) or heterocyclyl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy)}, heterocyclyl {itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy, C_{1-6} haloalkoxy, phenyl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy) or heterocyclyl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy)}, phenoxy {itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy, C_{1-6} haloalkoxy, phenyl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy) or heterocyclyl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy)}, SCN, CN, SO_3H (or an alkali metal salt thereof), methylenedioxy or difluoromethylenedioxy; when aryl is phenyl adjacent substituents may

join to form, together with the phenyl ring to which they are attached, a dihydrophenanthrene moiety;

d is 0, 1 or 2;

R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{37}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43} and R^{44} are, independently, hydrogen, C_{1-6} alkyl, aryl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy) or heterocyclyl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy);

R^{15}, R^{38}, R^{45} and R^{48} are, independently, C_{1-6} alkyl (optionally substituted by halogen, hydroxy or C_{3-10} cycloalkyl), C_{3-6} alkenyl, aryl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy) or heterocyclyl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy);

or an N-oxide thereof; or a pharmaceutically acceptable salt thereof; or a solvate thereof; have activity as pharmaceuticals, in particular as modulators of chemokine receptor (especially CCR3) activity, and may be used in the treatment of autoimmune, inflammatory, proliferative or hyperproliferative diseases, or immunologically-mediated diseases (including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS)).

In one aspect examples of these conditions are:

(1) (the respiratory tract) obstructive diseases of airways including: chronic obstructive pulmonary disease (COPD) (such as irreversible COPD); asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; bronchitis {such as eosinophilic bronchitis}; acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis; sarcoidosis; farmer's lung and related diseases; nasal polyposis; fibroid lung, idiopathic interstitial pneumonia, antitussive activity, treatment of chronic cough associated with inflammatory conditions of the airways or iatrogenic induced cough;

(2) (bone and joints) arthrides including rheumatic, infectious, autoimmune, seronegative spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis or Reiter's disease), Behçet's disease, Sjogren's syndrome or systemic sclerosis;

(3) (skin and eyes) psoriasis, atopic dermatitis, contact dermatitis or other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Phemphigus, bullous Phemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides erythemas, cutaneous eosinophilias, uveitis, Alopecia areata or vernal conjunctivitis;

(4) (gastrointestinal tract) Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease or food-related allergies which have effects remote from the gut (for example migraine, rhinitis or eczema);

(5) (Allograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea; or chronic graft versus host disease; and/or

(6) (other tissues or diseases) Alzheimer's disease, multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), Lupus disorders (such as lupus erythematosus or systemic lupus), erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, leprosy (such as lepromatous leprosy), Peridontal disease, Sezary syndrome, idiopathic thrombocytopenia pupura or disorders of the menstrual cycle.

In another aspect examples of these conditions are:

(1) (the respiratory tract) obstructive diseases of airways including: chronic obstructive pulmonary disease (COPD) (such as irreversible COPD); asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; bronchitis {such as eosinophilic bronchitis}; acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis; sarcoidosis; farmer's lung and related diseases; nasal polyposis; fibroid lung or idiopathic interstitial pneumonia;

(2) (bone and joints) arthrides including rheumatic, infectious, autoimmune, seronegative spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis or Reiter's disease), Behcet's disease, Sjogren's syndrome or systemic sclerosis;

(3) (skin and eyes) psoriasis, atopic dermatitis, contact dermatitis or other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Phemphigus, bullous Phemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides erythemas, cutaneous eosinophilias, uveitis, Alopecia areata or vernal conjunctivitis;

(4) (gastrointestinal tract) Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease or food-related allergies which have effects remote from the gut (for example migraine, rhinitis or eczema);

(5) (Allograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea; or chronic graft versus host disease; and/or

(6) (other tissues or diseases) Alzheimer's disease, multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), Lupus disorders (such as lupus erythematosus or systemic lupus), erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, leprosy (such as lepromatous leprosy), Peridontal disease, sezary syndrome, idiopathic thrombocytopenia pupura or disorders of the menstrual cycle.

In a further aspect examples of these conditions are:

(1) (the respiratory tract) obstructive diseases of airways including: chronic obstructive pulmonary disease (COPD) (such as irreversible COPD); asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; bronchitis {such as eosinophilic bronchitis}; acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis; sarcoidosis; farmer's lung and related diseases; nasal polyposis; fibroid lung or idiopathic interstitial pneumonia;

(2) (bone and joints) arthrides including rheumatic, infectious, autoimmune, seronegative spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis or Reiter's disease), Behcet's disease, Sjogren's syndrome or systemic sclerosis;

(3) (skin and eyes) psoriasis, atopic dermatitis, contact dermatitis or other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Phemphigus, bullous Phemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides erythemas, cutaneous eosinophilias, uveitis, Alopecia areata or vernal conjunctivitis;

(4) (gastrointestinal tract) Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease or food-related allergies which have effects remote from the gut (for example migraine, rhinitis or eczema);

(5) (Allograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea; or chronic graft versus host disease; and/or

(6) (other tissues or diseases) Alzheimer's disease, multiple sclerosis, atherosclerosis, Lupus disorders (such as lupus erythematosus or systemic lupus), erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, leprosy (such as lepromatous leprosy), Peridontal disease, sezary syndrome, idiopathic thrombocytopenia pupura or disorders of the menstrual cycle.

The compounds of formula (I) (as defined anywhere herein), (I'), (Ia"), (Ia), (Ia'), (Ib), (Ic), (Id), (Ie), (If) or (Ig), or a pharmaceutically acceptable salt thereof or a solvate thereof, are also H1 antagonists and may be used in the treatment of allergic disorders.

The compounds of formula (I) (as defined anywhere herein), (I'), (Ia"), (Ia), (Ia'), (Ib), (Ic), (Id), (Ie), (If) or (Ig), or a pharmaceutically acceptable salt thereof or a solvate thereof, may also be used to control a sign and/or symptom of what is commonly referred to as a cold (for example a sign and/or symptom of a common cold or influenza or other associated respiratory virus infection).

Thus, in a further aspect the present invention provides a compound of formula (I) (as defined anywhere herein), (I'), (Ia"), (Ia), (Ia'), (Ib), (Ic), (Id), (Ie), (If) or (Ig), or a pharmaceutically acceptable salt thereof or a solvate thereof, which is both a modulator of chemokine receptor (especially CCR3) activity and an H1 antagonist.

According to a further feature of the invention there is provided a compound of the formula (I) (as defined anywhere herein), (I'), (Ia"), (Ia), (Ia'), (Ib), (Ic), (Id), (Ie), (If) or (Ig), or a pharmaceutically acceptable salt thereof or a solvate thereof, for use in a method of treatment of a warm blooded animal (such as man) by therapy (including prophylaxis).

According to a further feature of the present invention there is provided a method for modulating chemokine receptor activity (especially CCR3 receptor activity) in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the formula (I) (as defined anywhere herein), (I'), (Ia"), (Ia), (Ia'), (Ib), (Ic), (Id), (Ie), (If) or (Ig) or a pharmaceutically acceptable salt thereof or a solvate thereof.

According to another feature of the present invention there is provided a method for antagonising H1 in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the formula (I) (as defined anywhere herein), (I'), (Ia"), (Ia), (Ia'), (Ib), (Ic), (Id), (Ie), (If) or (Ig), or a pharmaceutically acceptable salt thereof or a solvate thereof.

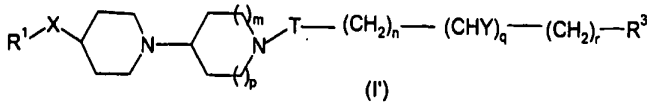
The invention also provides a compound of the formula (I) (as defined anywhere herein), (I'), (Ia"), (Ia), (Ia'), (Ib), (Ic), (Id), (Ie), (If) or (Ig), or a pharmaceutically acceptable salt thereof or a solvate thereof, for use as a medicament.

In another aspect the invention provides the use of a compound of formula (I) (as defined anywhere herein), (I'), (Ia"), (Ia), (Ia'), (Ib), (Ic), (Id), (Ie), (If) or (Ig), or a pharmaceutically acceptable salt thereof or a solvate thereof, in the manufacture of a medicament for use in therapy (for example modulating chemokine receptor activity (especially CCR3 receptor activity) or antagonising H1 in a warm blooded animal, such as man, or both).

In a further aspect the present invention provides the use of a compound of the formula (I), wherein: q, s and t are, independently, 0 or 1; n and r are, independently, 0, 1, 2, 3, 4 or 5; m and p are, independently, 0, 1 or 2; X is CH_2, C(O), O, S, S(O), $S(O)_2$ or NR^{37}; Y is NHR^2 or OH; T is C(O), C(S), $S(O)_2$ or CH_2; R^1 is hydrogen, C_{1-6} alkyl, aryl or heterocyclyl; R^2 and R^{47} are, independently, hydrogen, C_{1-6} alkyl, aryl(C_{1-4})alkyl or CO(C_{1-6} alkyl); R^3 is C_{1-6} alkyl {optionally substituted by halogen, CO_2R^4 or phthalimide}, C_{3-7} cycloalkyl {optionally substituted by C_{1-4} alkyl or oxo}, C_{3-7} cycloalkenyl {optionally substituted by oxo, C_{1-6} alkyl or aryl}, aryl or heterocyclyl; wherein, unless stated otherwise, the foregoing aryl and heterocyclyl moieties are optionally substituted by:

halogen, OH, SH, NO_2, oxo, C_{1-6} alkyl (itself optionally substituted by halogen, $OC(O)C_{1-6}$ alkyl, $S(O)_2R^{48}$, phenyl (itself optionally substituted by halo (such as one or two chlorine or fluorine atoms), C_{1-6} alkyl, $S(O)_2R^{38}$ or $C(O)NR^{39}R^{40}$), naphthyloxy (itself optionally substituted by halo or C_{2-6} alkenyl), C_{3-10} cycloalkyl (itself optionally substituted by C_{1-4} alkyl or oxo) or $NR^{41}C(O)OCH_2$(fluoren-9-yl)), $NR^{41}C(O)OCH_2$(fluoren-9-yl), C_{1-6} alkoxy (itself optionally substituted by halogen, C_{1-6} alkoxy, $NHCO_2(C_{1-6}$ alkyl), CO_2R^4, NR^5R^6 or phenyl (itself optionally substituted by halogen or NO_2)), C_{1-6} alkylthio, C_{1-6} haloalkylthio, C_{3-10} cycloalkyl, NR^7R^8, $NR^9C(O)R^{10}$, CO_2R^{11}, $C(O)NR^{12}R^{13}$, $C(O)R^{14}$, $S(O)_dR^{15}$, $S(O)_2NR^{42}R^{43}$, $NR^{44}S(O)_2R^{45}$, phenyl (itself optionally substituted by halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2 or C_{1-6} alkoxy (itself optionally substituted by halo, OH or pyridinyl)), heterocyclyl (itself optionally substituted by halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy), phenoxy (itself optionally substituted by halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy), SCN, CN, SO_3H (or an alkali metal salt thereof) or methylenedioxy; when aryl is phenyl adjacent substituents may join to form, together with the phenyl ring to which they are attached, a dihydrophenanthrene moiety; d is 0, 1 or 2; R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{37}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43} and R^{44} are, independently, hydrogen, C_{1-6} alkyl or aryl (itself optionally substituted by halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy); R^{15}, R^{38}, R^{45} and R^{48} are, independently, C_{1-6} alkyl (optionally substituted by halogen, hydroxy or C_{3-10} cycloalkyl) or aryl (itself optionally substituted by halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy); or a pharmaceutically acceptable salt thereof; or a solvate thereof; in the manufacture of a medicament for use in therapy (for example modulating chemokine receptor activity (especially CCR3 receptor activity) or antagonising H1 in a warm blooded animal, such as man, or both).

In another aspect the present invention provides the use of a compound of the formula (I'):



(I')

wherein: q is 0 or 1; n and r are, independently, 0, 1, 2, 3, 4 or 5; m and p are, independently, 0, 1 or 2; X is CH_2, CO, O, S, S(O), $S(O)_2$ or NR^{37}; Y is NHR^2 or OH; T is CO, CS, SO_2 or CH_2; R^1 is hydrogen, C_{1-6} alkyl, aryl or heterocyclyl; R^2 is hydrogen, C_{1-6} alkyl, aryl(C_{1-4})alkyl or $CO(C_{1-6}$ alkyl); R^3 is C_{1-6} alkyl {optionally substituted by halogen, CO_2R^4 or phthalimide}, C_{3-7} cycloalkyl {optionally substituted by C_{1-4} alkyl or oxo}, C_{3-7} cycloalkenyl {optionally substituted by C_{1-6} alkyl or aryl}, aryl or heterocyclyl; wherein, unless stated otherwise, the foregoing aryl and heterocyclyl moieties are optionally substituted by: halogen, OH, SH, NO_2, oxo, C_{1-6} alkyl (itself optionally substituted by halogen, $OC(O)C_{1-6}$ alkyl, phenyl (itself optionally substituted by halo (such as one or two chlorine or fluorine atoms), C_{1-6} alkyl, SO_2R^{38} or $CONR^{39}R^{40}$), naphthyloxy (itself optionally substituted by halo or C_{2-6} alkenyl) or $NR^4C(O)OCH_2$(fluoren-9-yl)), $NR^{41}C(O)OCH_2$(fluoren-9-yl), C_{1-6} alkoxy (itself optionally substituted by halogen, CO_2R^4, NR^5R^6 or phenyl (itself optionally substituted by halogen or NO_2)), C_{1-6} alkylthio, nitro, C_{3-7} cycloalkyl, NR^7R^8, NR^9COR^{10}, CO_2R^{11}, $CONR^{12}R^{13}$, COR^{14}, SO_dR^{15}, $SO_2NR^{42}R^{43}$, $NR^{44}SO_2R^{45}$, phenyl (itself optionally substituted by halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2 or C_{1-6} alkoxy (itself optionally substituted by halo, OH or pyridinyl)), heterocyclyl (itself optionally substituted by halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy), phenoxy (itself optionally substituted by halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy), SCN, CN, SO_3H (or an alkali metal salt thereof) or methylenedioxy; when aryl is phenyl adjacent substituents may join to form, together with the phenyl ring to which they are attached, a dihydrophenanthrene moiety; d is 0, 1 or 2; R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{37}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43} and R^{44} are, independently, hydrogen, C_{1-6} alkyl or aryl (itself optionally substituted by halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy); R^{15}, R^{38} and R^{45} are, independently, C_{1-6} alkyl or aryl (itself optionally substituted by halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy); or a pharmaceutically acceptable salt thereof; or a solvate thereof; in the manufacture of a medicament for use in therapy (for example modulating chemokine receptor activity (especially CCR3 receptor activity) in a warm blooded animal, such as man).

The invention further provides the use of a compound of formula (I) (as defined anywhere above), (I'), (Ia"), (Ia), (Ia'), (Ib), (Ic), (Id), (Ie), (If) or (Ig), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of:

(1) (the respiratory tract) obstructive diseases of airways including: chronic obstructive pulmonary disease (COPD) (such as irreversible COPD); asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; bronchitis {such as

eosinophilic bronchitis}; acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis; sarcoidosis; farmer's lung and related diseases; nasal polyposis; fibroid lung, idiopathic interstitial pneumonia, antitussive activity, treatment of chronic cough associated with inflammatory conditions of the airways or iatrogenic induced cough;

(2) (bone and joints) arthrides including rheumatic, infectious, autoimmune, seronegative spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis or Reiter's disease), Behcet's disease, Sjogren's syndrome or systemic sclerosis;

(3) (skin and eyes) psoriasis, atopic dermatitis, contact dermatitis or other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Phemphigus, bullous Phemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides erythemas, cutaneous eosinophilias, uveitis, Alopecia areata or vernal conjunctivitis;

(4) (gastrointestinal tract) Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease or food-related allergies which have effects remote from the gut (for example migraine, rhinitis or eczema);

(5) (Allograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea; or chronic graft versus host disease; and/or

(6) (other tissues or diseases) Alzheimer's disease, multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), Lupus disorders (such as lupus erythematosus or systemic lupus), erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, leprosy (such as lepromatous leprosy), Peridontal disease, sezary syndrome, idiopathic thrombocytopenia pupura or disorders of the menstrual cycle;

in a warm blooded animal, such as man.

In a further aspect a compound of formula (I) (as defined anywhere above), (I'), (Ia"), (Ia), (Ia'), (Ib), (Ic), (Id), (Ie), (If) or (Ig), or a pharmaceutically acceptable salt thereof, is useful in the treatment of asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or

airways hyper-responsiveness)}; or rhinitis {including acute, allergic, atrophic or chronic rhinitis, such as rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis}.

In a still further aspect a compound of formula (I) (as defined anywhere above), (I'), (Ia"), (Ia), (Ia'), (Ib), (Ic), (Id), (Ie), (If) or (Ig), or a pharmaceutically acceptable salt thereof, is useful in the treatment of asthma.

The invention also provides the use of a compound of formula (I) (as defined anywhere above), (I'), (Ia"), (Ia), (Ia'), (Ib), (Ic), (Id), (Ie), (If) or (Ig), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of a sign and/or symptom of what is commonly referred to as a cold (for example a sign and/or symptom of common cold or influenza or other associated respiratory virus infection).

The present invention also provides a the use of a compound of formula (I) (as defined anywhere above), (I'), (Ia"), (Ia), (Ia'), (Ib), (Ic), (Id), (Ie), (If) or (Ig), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of asthma or rhinitis.

The present invention further provides a method of treating a chemokine mediated disease state (especially a CCR3 mediated disease state, especially asthma) or an H1 mediated disease state (such as an allergic disorder) in a warm blooded animal, such as man, which comprises administering to a mammal in need of such treatment an effective amount of a compound of formula (I), (I'), (Ia"), (Ia), (Ia'), (Ib), (Ic), (Id), (Ie), (If) or (Ig), or a pharmaceutically acceptable salt thereof or solvate thereof.

The present invention also provides a method of treating a sign and/or symptom of a cold (for example a sign and/or symptom of common cold or influenza or other associated respiratory virus infection) in a warm blooded animal, such as man, which comprises administering to a mammal in need of such treatment an effective amount of a compound of formula (I), (I'), (Ia"), (Ia), (Ia'), (Ib), (Ic), (Id), (Ie), (If) or (Ig), or a pharmaceutically acceptable salt thereof or solvate thereof.

In order to use a compound of the invention, or a pharmaceutically acceptable salt thereof or solvate thereof, for the therapeutic treatment of a warm blooded animal, such as man, in particular modulating chemokine receptor (for example CCR3 receptor) activity or

antagonising H1, said ingredient is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

The present invention further provides a method of treating a chemokine mediated disease state (especially a CCR3 mediated disease state, especially asthma) in a warm blooded animal, such as man, which comprises administering to a mammal in need of such treatment an effective amount of a compound of formula (I), (I'), (Ia"), (Ia), (Ia'), (Ib), (Ic), (Id), (Ie), (If) or (Ig), or a pharmaceutically acceptable salt thereof or solvate thereof.

In order to use a compound of the invention, or a pharmaceutically acceptable salt thereof or solvate thereof, for the therapeutic treatment of a warm blooded animal, such as man, in particular modulating chemokine receptor (for example CCR3 receptor) activity, said ingredient is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula (I), (I'), (Ia"), (Ia), (Ia'), (Ib), (Ic), (Id), (Ie), (If) or (Ig), or a pharmaceutically acceptable salt thereof or a solvate thereof (active ingredient), and a pharmaceutically acceptable adjuvant, diluent or carrier. In a further aspect the present invention provides a process for the preparation of said composition which comprises mixing active ingredient with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by topical (such as to the lung and/or airways or to the skin), oral, rectal or parenteral administration. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, aerosols, dry powder formulations, tablets, capsules, syrups, powders, granules, aqueous or oily solutions or suspensions, (lipid) emulsions, dispersible powders, suppositories, ointments, creams, drops and sterile injectable aqueous or oily solutions or suspensions.

A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 0.1mg and 1g of active ingredient.

In another aspect a pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection.

Each patient may receive, for example, an intravenous, subcutaneous or intramuscular dose of 0.01mgkg^{-1} to 100mgkg^{-1} of the compound, preferably in the range of 0.1mgkg^{-1} to 20mgkg^{-1} of this invention, the composition being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively the intravenous dose may be given by continuous infusion over a period of time. Alternatively each patient will receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

The following illustrate representative pharmaceutical dosage forms containing the compound of formula (I), (I'), (Ia"), (Ia), (Ia'), (Ib), (Ic), (Id), (Ie), (If) or (Ig), or a pharmaceutically-acceptable salt thereof (hereafter Compound X), for therapeutic or prophylactic use in humans:

(a)

Tablet I	mg/tablet
Compound X	100
Lactose Ph.Eur.	179
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(b)

Tablet II	mg/tablet
Compound X	50
Lactose Ph.Eur.	229
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(c)

Tablet III	mg/tablet
Compound X	1.0
Lactose Ph.Eur.	92
Croscarmellose sodium	4.0
Polyvinylpyrrolidone	2.0
Magnesium stearate	1.0

(d)

Capsule	mg/capsule
Compound X	10
Lactose Ph.Eur.	389
Croscarmellose sodium	100
Magnesium stearate	1.0

(e)

Injection I	(50 mg/ml)
Compound X	5.0% w/v
Isotonic aqueous solution	to 100%

Buffers, pharmaceutically-acceptable cosolvents such as polyethylene glycol, polypropylene glycol, glycerol or ethanol or complexing agents such as hydroxy-propyl β-cyclodextrin may be used to aid formulation.

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) when given, ^{1}H NMR data is quoted and is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300MHz or 400MHz using perdeuterio DMSO-D6

(CD_3SOCD_3) or $CDCl_3$ as the solvent unless otherwise stated;

(ii) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (CI) mode using a direct exposure probe; where indicated ionisation was effected by electron impact (EI) or fast atom bombardment (FAB); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$;

(iii) the title and sub-titled compounds of the examples and methods were named using the AUTONOM program from Beilstein informationssysteme GmbH;

(iv) unless stated otherwise, reverse phase HPLC was conducted using a Symmetry, NovaPak or Ex-Terra reverse phase silica column; and

(v) the following abbreviations are used:

RPHPLC	reverse phase HPLC
RT	room temperature
DEAD	diethyl-azodicarboxylate
NMP	N-methylpyrrolidone
CDI	N,N'-carbonyl diimidazole
MTBE	tert-butyl methyl ether
DMF	N,N-dimethylformamide
Boc or BOC	tert-butoxycarbonyl
HPLC	high pressure liquid chromatography
PYBROP™	bromo-tris-pyrrolidino-phosphonium hexafluorophosphate

THF	tetrahydrofuran
DCM	dichloromethane
TFA	trifluoroacetic acid
m.pt.	melting point
DMSO	dimethylsulfoxide
Ac	Acetate
aq	aqueous
IPA	iso-propyl alcohol
equiv.	equivalents

Example 1

This Example illustrates the preparation of 4-(3,4-dichlorophenoxy)piperidine.

Step a: *tert*-Butyl 4-(3,4-dichlorophenoxy)-1-piperidinecarboxylate

Diethyl azodicarboxylate (41.0ml) was added to a solution of triphenylphosphine (62.9g) in tetrahydrofuran (800ml) at 0°C. After 15 minutes 3,4-dichlorophenol (39.1g) was added, after a further 15 minutes *tert*-butyl 4-hydroxy-1-piperidinecarboxylate (48.3g) in tetrahydrofuran (400ml) was added dropwise over 30 min. The solution was stirred at room temperature for 16 hours and concentrated to a small volume. Purification by

chromatography (ethyl acetate : *iso*-hexane 95:5) gave the sub-title compound as an oil (61.3g).

MS: APCI(+ve): 246 (M-BOC+2H)

Step b: 4-(3,4-Dichlorophenoxy)piperidine

The product from Step a was dissolved in dichloromethane (600ml) and trifluoroacetic acid (300ml) was added. After 24 hours at room temperature the solution was evaporated and the resultant gum triturated under ether to give the sub-titled product as a solid (36.6g). The free base was liberated by addition of aqueous NaOH (2M) and extraction with ethyl acetate followed by evaporation of solvent to give the title compound as a gum (25g).

^{1}H NMR: δ($CDCl_3$) 1.77 (1H, br s), 2.05-2.26 (4H, m), 3.20-3.49 (4H, m), 4.61 (1H, s), 6.69-7.52 (3H, m).

Example 2

This Example illustrates the preparation of [4-(3,4-dichloro-phenoxy)-[1,4']bipiperidinyl-1'-yl]-(3-methanesulfonyl-phenyl)-methanone acetate (acetate salt of Compound 281 in Table I).

Step a: 4-(3,4-Dichloro-phenoxy)-[1,4']bipiperidinyl-1'-carboxylic acid *tert*-butyl ester

4-(3,4-Dichlorophenoxy)piperidine (1.5g) was dissolved in 1,2-dichloroethane (21ml). 1-Boc-4-piperidone was added (1.21g) followed by $NaBH(OAc)_3$ (1.81g) and acetic acid (0.37g). After 18 hours at room temperature aqueous NaOH (1M) solution and diethyl ether were added. The product was extracted with diethyl ether, the combined organic extracts dried with $MgSO_4$ and concentrated. Purification by silica chromatography (dichloromethane : methanol 92:8) gave the sub-title product (1.97g).

MS: APCI(+ve): 429 (M+H)

Step b: 4-(3,4-Dichloro-phenoxy)-[1,4']bipiperidine

The product of Step a was dissolved in dichloromethane (30ml) and trifluoroacetic acid (15ml) was added. After 4 hours at room temperature the solution was evaporated and the resultant gum triturated under ether to give the trifluoroacetate salt of the sub-titled product as a solid (1.15g). The free base was liberated by addition of aqueous NaOH (2M) and extraction with ethyl acetate followed by evaporation of solvent to give the sub-title compound as a solid (0.68g).

^{1}H NMR: δ($CDCl_3$) 1.38-1.51 (2H, m), 1.74-2.02 (6H, m), 2.38-2.50 (3H, m), 2.56-2.61 (2H, m), 2.79-2.86 (2H, m), 3.14-3.18 (2H ,m), 4.22-4.28 (1H, m), 6.73-7.32 (3H, m).

Step c: [4-(3,4-Dichloro-phenoxy)-[1,4']bipiperidinyl-1'-yl]-(3-methanesulfonyl-phenyl)-methanone acetate

The product of Step b (0.15g) was dissolved in THF (4ml), bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PYBROP™; 0.235g), 3-methylsulphonylbenzoic acid (0.091g) and N,N-di-*iso*-propylethylamine (0.238ml) were added. After 18 hours at room temperature ethyl acetate and aqueous $NaHCO_3$ solution were added. The product was extracted with ethyl acetate, the combined organic extracts dried with Na_2SO_4 and concentrated. Purification by reverse phase HPLC (with a gradient eluent system (45% $MeCN/NH_4OAc_{aq}$ (0.1%) to 95% $MeCN//NH_4OAc_{aq}$ (0.1%)) gave the title compound (0.095g).

^{1}H NMR: δ(DMSO-D6) 1.44-1.94 (8H, m), 2.37-2.77 (5H, m), 3.07-3.55 (6H, m), 4.40 (1H, m), 4.50-4.53 (1H, m), 6.96-8.02 (7H, m).

Melting point: 60-61°C becomes a gum.

Melting point of free base: 154°C.

Example 3

This Example illustrates the preparation of (4-amino-3-methoxy-phenyl)-[4-(3,4-dichlorophenoxy)-[1,4']bipiperidinyl-1'-yl]-methanone acetate (Compound 282 of Table I).

The compound was prepared by the method of Example 2, Step c using 4-amino-3-methoxybenzoic acid to give the title compound as a solid (0.016g).

^{1}H NMR: δ(DMSO-D6) 1.32-2.01 (8H, m), 2.28-2.88 (5H, m), 3.32 (4H, br s), 3.77 (3H , s), 4.13 (2H, br s), 4.39-4.44 (1H, m), 6.59-7.50 (6H, m).

Melting point: 171°C becomes a gum.

Example 4

This Example illustrates the preparation of (4-amino-3-methoxy-phenyl)-{3-[4-(3,4-difluoro-phenoxy)-piperidin-1-yl]-pyrrolidin-1-yl}-methanone (Compound 4 of Table II).

Step a: *tert*-Butyl 4-(3,4-difluorophenoxy)-1-piperidinecarboxylate

This compound was prepared according to the method of Example 1 Step a using 3,4-difluorophenol to afford the compound as an oil (5.4g).

MS: ESI(+ve): 213 (M-BOC+H)

Step b: 4-(3,4-Difluorophenoxy)piperidine

This compound was prepared according to the method of Example 1 Step b to afford the compound as a pale yellow oil (3g).

MS: ESI(+ve): 214 (+H)

Step c: 3-[4-(3,4-Difluoro-phenoxy)piperidin-1-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

The product of Step b (0.5g) was dissolved in 1,2-dichloroethane (7ml). *tert*-Butyl 3-oxo-1-pyrrolidinecarboxylate (0.43g) was added followed by $NaBH(OAc)_3$ (0.7g) and acetic acid (0.08g). After 24 hours at room temperature aqueous NaOH (1M) solution and diethyl ether were added. The product was extracted with diethyl ether, the combined organic extracts dried with $MgSO_4$ and concentrated. Purification by silica chromatography (100% ethyl acetate) gave the sub-title product (0.79g).

MS: ESI(+ve): 383 (M+H)

Step d: 3,4-Difluorophenyl 1-(3-pyrrolidinyl)-4-piperidinyl ether

The product of Step c was dissolved in dioxane (10ml) and HCl (6N) (10ml) was added and the reaction stirred for 3 hrs. Organic solvent was evaporated and aqueous NaOH (2M) added. The product was extracted with ethyl acetate, the combined organic extracts dried with Na_2SO_4 and concentrated to give the sub-title product as an oil (0.54g).

^{1}H NMR: δ($CDCl_3$) 1.60-2.39 (9H, m), 2.70-3.13 (6H, m), 4.19-4.22 (1H, m), 6.58-7.52 (3H, m).

Step e: (4-Amino-3-methoxy-phenyl)-{3-[4-(3,4-difluoro-phenoxy)-piperidin-1-yl]-pyrrolidin-1-yl}-methanone

This compound was prepared by the method of Example 2 Step c using 4-amino-3-methoxybenzoic acid to give the title compound as a solid (0.151g).

^{1}H NMR: δ($CDCl_3$) 1.95-2.43 (5H, m), 2.69-2.81 (3H, m), 3.42-3.91 (10H, m), 4.19-4.23 (1H, m), 6.56-7.25 (6H, m).

Melting point: 138-139°C.

Example 5

This Example illustrates the preparation of (4-amino-3-methoxy-phenyl)-[4-(3,4-difluoro-phenoxy)-[1,4']bipiperidinyl-1'-yl]-methanone (Compound 1 in Table II).

Step a: 4-(3,4-Difluoro-phenoxy)-[1,4']bipiperidinyl-1'-carboxylic acid *tert*-butyl ester

This compound was prepared by the method of Example 2, Step a using 4-(3,4-difluorophenoxy)piperidine to give the sub-title compound as a solid (0.48g).

MS: APCI(+ve): 397 (M+H)

Step b: 4-(3,4-Difluoro-phenoxy)-[1,4']bipiperidinyl

This compound was prepared by the method of Example 2, Step b to give the sub-title compound as a solid (0.36g).

MS: APCI(+ve): 297 (M+H)

Step c: (4-Amino-3-methoxy-phenyl)-[4-(3,4-difluoro-phenoxy)-[1,4']bipiperidinyl-1'-yl]-methanone

This compound was prepared by the method of Example 2, Step c using 4-amino-3-methoxybenzoic acid to give the title compound as a gum (0.133g).

^{1}H NMR: δ($CDCl_3$) 1.50-1.60 (2H, m), 1.85-1.93 (4H, m), 2.04-2.08 (2H, m), 2.58-2.62 (2H, m), 2.69-2.75 (1H, m), 2.86-2.90 (4H, m), 3.86 (3H, s), 3.86 (2H, m), 4.25-4.30 (1H, m), 6.50-6.61 (1H , m), 6.65 (1H, dd), 6.70-6.75 (1H. m), 6.85 (1H, dt), 6.94 (1H, s), 7.01-7.09 (1H, m).

Example 6

This Example illustrates the preparation of (4-amino-3-methoxy-phenyl)-[4-(3,4-difluoro-phenoxy)-[1,3']bipiperidinyl-1'-yl]-methanone (Compound 2 in Table II).

Step a: 4-(3,4-Difluoro-phenoxy)-[1,3']bipiperidinyl-1'-carboxylic acid *tert*-butyl ester

This compound was prepared by the method of Example 2, Step a using 3-oxo-piperidine-1-carboxylic acid *tert*-butyl ester to give the sub-title compound as a solid (0.946g).

MS: APCI(+ve): 397 (M+H)

Step b: 4-(3,4-Difluoro-phenoxy)-[1,3']bipiperidinyl

This compound was prepared by the method of Example 2, Step b to give the sub-title compound as a solid (0.706).

MS: ESI(+ve): 297 (M+H)

Step c: (4-Amino-3-methoxy-phenyl)-[4-(3,4-difluoro-phenoxy)-[1,3']bipiperidinyl-1'-yl]-methanone

This compound was prepared by the same method as Example 2, Step c using 4-amino-3-methoxybenzoic acid to give the title compound as a gum (0.070g).

^{1}H NMR: δ($CDCl_3$) 1.41-1.67 (4H, m), 1.73-1.80 (2H, m), 1.86-2.00 (2H, m), 2.44 (3H, m), 3.00-3.13 (2H, m), 2.79-2.91 (2H, m), 3.82 (3H, s), 3.97-4.01 (1H, d), 4.14-4.17 (1H, d), 4.32 (1H, sept), 4.89 (2H, s), 6.67 (1H, d), 6.75-6.79 (1H, m), 6.80 (1H, dd), 6.87 (1H, s), 6.98-7.06 (1H, m), 7.27 (1H, q).

Example 7

This Example illustrates the preparation of 4-(3,4-dichloro-phenoxy)-1'-(5-pyridin-2-yl-thiophene-2-sulfonyl)-[1,4']bipiperidinyl (Compound 280 in Table I).

The product of Example 2, Step b (0.2g) was dissolved in acetone (4ml). Potassium carbonate [0.134g dissolved in H_2O (1.2ml)] was then added, followed by 5-pyridin-2-yl-thiophene-2-sulfonyl chloride (0.168g) and the reaction left to stir for 1 hr. Water was then added and the product extracted with ethyl acetate. The combined organic extracts dried with Na_2SO_4 and concentrated. Purification reverse phase HPLC (with a gradient eluent system (25% MeCN/NH_4OAc_{aq} (0.1%) to 95% MeCN//NH_4OAc_{aq} (0.1%)) gave the title compound as a solid (0.077g).

^{1}H NMR: δ(DMSO-D6) 1.45-1.58 (4H, m), 1.79-1.90 (4H, m), 2.28-2.46 (5H, m), 2.66-2.73 (2H, m), 3.67-3.71 (2H, m), 4.35-4.43 (1H, m), 6.93-8.60 (9H, m).

Melting point: 139-140°C.

Example 8

This Example illustrates the preparation of 4-(3,4-difluoro-phenoxy)-1'-(5-pyridin-2-yl-thiophene-2-sulfonyl)-[1,4']bipiperidinyl (Compound 3 in Table II).

This compound was prepared by the method of Example 7 using product of Example 5, step b to give the title compound as a solid (0.095g).

^{1}H NMR: δ($CDCl_3$) 1.67-1.80 (4H, m), 1.87-2.01 (1H, t), 2.30 (1H, t), 2.39-2.50 (2H, m), 2.74-2.78 (2H, m), 3.89 (2H, d), 4.16-4.20 (1H, m), 6.56-6.60 (1H, m), 6.67-6.63 (1H, m), 7.03 (1H, q), 7.26 (1H, t), 7.52 (1H, d), 7.53 (1H, d), 7.70 (1H, d), 7.76 (1H, dt), 8.60 (1H, d).

Melting point: 128-129°C.

Example 9

This Example illustrates the preparation of [4-(3,4-dichloro-phenoxy)-[1,4']bipiperidinyl-1'-yl]-(2-methanesulfonyl-phenyl)-methanone (Compound 293 Table I).

Step 1: Preparation of 4-hydroxy-[1,4']bipiperidinyl-1'-carboxylic acid tert-butyl ester

To 1-tert-butoxycarbonyl-4-piperidone (200g, 1.01mol) in tetrahydrofuran (THF) (1500ml) was added 4-hydroxypiperidine (78.1g, 0.77mol). The resultant slurry was stirred for 30 minutes before cooling the reaction mixture with ice/water, acetic acid (47ml) is then added (exotherm) which caused precipitation. The slurry was allowed to warm to room temperature before the addition of sodium triacetoxyborohydride (236g, 1.12mol) which was washed in with THF (500ml). The resultant slurry was stirred

overnight at room temperature. To the reaction mixture was added water (2000ml) to give a solution. The solution was then extracted with diethyl ether (3 x 1800ml). The aqueous phase was basified with 10% aq NaOH (950ml) and extracted with dichloromethane (DCM) (3 x 1500ml). The combined DCM layers are dried ($MgSO_4$), filtered and the solvent removed to give the sub-titled compound as a yellow viscous oil, (177g, 81%; MS: (M+H) 285).

Step 2: Preparation of 4-(3,4-dichlorophenoxy)-[1,4']bipiperidinyl-1'-carboxylic acid tert-butyl ester

To a solution of potassium tert-butoxide (139.0g, 1.24mol) in THF (500ml) was added a solution of the product of Step 1 (176.2g, 0.62mol) in THF (1000ml). The reaction mixture was stirred 10 minutes before the additon of 3,4 dichlorofluorobenzene (122.8g, 0.74mol), this caused a green colouration that subsequently faded. The reaction mixture was then heated at reflux for 90 minutes. The reaction mixture was then cooled to room temperature before the addition of saturated $NaHCO_3$ (1600ml). The layers were separated and the organic layer stripped to leave an orange semi-solid. The solid was dissolved in DCM (1500ml) and dried ($MgSO_4$), filtered and the solvent removed. To the resultant solid was added methyl tert-butyl ether (MTBE) (54ml) and iso-hexane (1000ml) to give a slurry which was stirred overnight. The slurry was then filtered and washed with isohexane (200ml) and the solid dried *in vacuo* at 50°C to give the sub-titled compound as a pale powder, (211.6g, 80%; MS: (M+H) 429).

Step 3: Preparation of 4-(3,4-dichlorophenoxy)-[1,4']bipiperidine

The product of Step 2 (10.15g, 23.6mmol) was dissolved in dichloromethane (150ml) and trifluoroacetic acid (40ml, 519mmol) added and the resultant solution stirred. After 90 minutes the dichloromethane and trifluoroacetic acid were removed on a rotary evaporator. The resultant oil was partitioned between ethyl acetate (100ml) and 2M aq NaOH (100ml). The layers were separated and the organics extracted with 10% aq citric acid (100ml). The layers were separated and the aqueous basified with 2M aq NaOH and extracted with ethyl acetate (200ml). The organics were dried ($MgSO_4$), filtered and the solvent removed to give the sub-titled product as a pale oil which solidified on standing (4.62g, 59%; MS: (M+H) 329).

Step 4: Preparation of [4-(3,4-dichloro-phenoxy)-[1,4']bipiperidinyl-1'-yl]-(2-methanesulfonyl-phenyl)-methanone

Oxalyl chloride (55ml, 0.63mol) was added dropwise over 10 minutes to a stirred suspension of 2-methanesulfonyl-benzoic acid (7.1g, 0.036) in DCM (550ml) containing DMF (0.5ml). The solution was then stirred for 2 hours at room temperature. The solution was then evaporated to give a solid that was redissolved in dichloromethane and again evaporated to give a yellow solid. The solid acid chloride was dissolved in DCM (275ml) and was added over 10 minutes to a stirred solution of the product of Step 3 (11.0g, 0.033mol) and triethylamine (15.4ml, 0.11mol) in dichloromethane (125ml). The resultant solution was stirred at room temperature for 16 hours. The solution was then washed with water (500ml), 1M aq NaOH (500ml) and water (2 x 500ml). The organic phase was dried ($MgSO_4$), filterered and the solvent removed to give a pale yellow foam. The foam was triturated with diethyl ether to give the title compound (12.96g, 76%).

Melting point 141°C.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 1.39 - 1.63 (1H, m), 1.72 - 2.04 (6H, m), 2.42 - 2.68 (2H, m), 2.73 - 2.92 (3H, m), 3.00 - 3.08 (1H, m), 3.23 (1H, s), 3.28 (2H, s), 3.34 - 3.40 (1H, m), 3.46 - 3.52 (1H, m), 4.21 - 4.30 (1H, m), 4.62 - 4.68 (1H, m), 4.80 - 4.86 (1H, m), 6.72 - 6.76 (1H, m), 6.97 - 7.00 (1H, m), 7.28 - 7.32 (1H, m), 7.32-7.37 (1H, m), 7.56 - 7.61 (1H, m), 7.64 - 7.70 (1H, m), 8.05 - 8.10 (1H, m).

Example 10

This Example illustrates the preparation of [4-(3,4-dichloro-phenoxy)-[1,4']bipiperidinyl-1'-yl]-(3-methanesulfonyl-phenyl)-methanone (Compound 281 Table I).

Oxalyl chloride (30mls, 0.35mol) was added dropwise over 10 minutes to a stirred suspension of 3-methanesulfonyl-benzoic acid (6g, 0.03) in DCM (300ml) containing DMF (0.3ml). The solution was then stirred for 4 hours at room temperature. The solution was then evaporated under high vacuum to give a solid which was redissolved in dichloromethane and again evaporated to give a yellow solid. The solid acid chloride was dissolved in DCM (100ml) and was added over 10 minutes to a stirred solution of the product of step 3 of Example 9 (9.3g, 0.028mol) and triethylamine (8.4ml, 0.06mol) in dichloromethane (100ml). The resultant solution was stirred at room temperature for 3 hours. The solution was then washed with water (100ml), 1M aq NaOH (2 x 100ml) and water (2 x 100ml). The organic phase was dried ($MgSO_4$), filterered and the solvent removed to give a pale yellow foam. The foam was dissolved in methanol (100ml) and

allowed to crystallise. The crystals were filtered, washed with methanol and then dried to give the title compound (12.2g, 84%).

Melting point 157°C.

^{1}H NMR: (400MHz, $CDCl_3$) δ 1.40 - 1.65 (2H, m), 1.75 - 1.85 (3H, m), 1.93 - 2.03 (3H, m), 2.42 - 2.51 (2H, m), 2.58 (1H, tt), 2.74 - 2.91 (3H, m), 3.00 - 3.14 (1H, m), 3.07 (3H, s), 3.62 - 3.76 (1H, m), 4.27 (1H, septet), 4.69 - 4.80 (1H, m), 6.75 (1H, dd), 6.99 (1H, d), 7.31 (1H, d), 7.64 (1H, t), 7.69 (1H, dt), 7.97 - 7.98 (1H, m), 8.00 (1H, dt).

The hydrochloride salt (melting point 159°C) was prepared by evaporation to dryness of a clear solution of Compound 281 of Table I and HCl in ethanol.

Example 11

This Example illustrates the preparation of [4-(3,4-dichloro-phenoxy)-[1,4']bipiperidinyl-1'-yl]-(2-methanesulfonyl-thiophen-5-yl)-methanone (Compound 332 of Table I).

Oxalyl chloride (32ml, 0.37mol) was added dropwise over 10 minutes to a stirred suspension of 5-(methylsulfonyl)-2-thiophenecarboxylic acid (6.64g, 0.032) in DCM (300ml) containing DMF (0.3ml). The solution was then stirred for 2 hours at room temperature. The solution was then removed to give a solid which was redissolved in dichloromethane and the solvent again removed to give a yellow solid. The solid acid chloride was dissolved in DCM (150ml) and was added over 10 minutes to a stirred solution of the product of step 3 of Example 9 (10g, 0.03mol) and triethylamine (9ml, 0.065mol) in dichloromethane (300ml). The resultant solution was stirred at room temperature for 2 hours. The solution was then washed with water (100ml), 1M aq NaOH (2 x 100ml) and water (300ml). The organic phase was dried ($MgSO_4$), filterered and the solvent removed to give an orange foam. The solid was dissolved in dichloromethane (200ml) and purified by chromatography using ethyl acetate and then acetone as the eluant. The purified material was precipitated from acetone by the addition of iso-hexane. The crystals were filtered, washed with isohexane and then dried to give the title compound (11.5g, 74%).

Melting point: 153-154°C.

^{1}H NMR (399.98 MHz, DMSO-D6) δ 1.42 - 1.48 (2H, m), 1.56 - 1.62 (2H, m), 1.77 - 1.84 (2H, m), 1.90 - 1.96 (2H, m), 2.37 - 2.43 (2H, m), 2.56 - 2.63 (2H, m), 2.75 -

2.80 (2H, m), 2.89 - 3.14 (2H, m), 3.29 - 3.32 (1H, m), 3.41 (3H, s), 4.41 - 4.45 (1H, m), 6.98 (1H, dd), 7.25 (1H, d), 7.49 (2H, q), 7.77 (1H, d).

Example 12

This Example illustrates the preparation of [4-(4-chloro-2-methyl-phenoxy)-[1,4']bipiperidinyl-1'-yl]-(3-methanesulfonyl-phenyl)-methanone (Compound 1 of Table IV)

A solution of 4-(2-methyl-4-chloro-phenoxy)-piperidine (0.87mmol) and 1-(3-methanesulfonyl-benzoyl)-piperidin-4-one (0.925mmol) in NMP (5ml) and glacial acetic acid (1mmol) was stirred at room temperature for 1hour after which sodium triacetoxy borohydride (2mmol) was added. The resulting mixture was stirred at RT for 24hours, evaporated on to silica (2g) and placed on to a Mega Bond elut cartridge (10g Silica). The product was eluted with DCM/MeOH mixtures and further purified by Reverse Phase preparative chromatography, MeOH/aqueous TFA gradient on a Symmetry column. The free base was isolated by dissolving in EtOAc and washing with sodium bicarbonate solution, drying the organic layer with $MgSO_4$ and evaporation left the product as a white solid (0.047g; M.pt. 83-84°C).

^{1}H NMR (300MHz, DMSO-D6) δ 1.2-2.8 (bm, 14H), 2.15 (s, 3H), 3.1 (bm, 1H), 3.25 (s, 3H), 3.5 (bm, 1H), 4.4 (bm, 1H), 4.5(bm, 1H), 7.0 (d, 1H), 7.12 (m, 1H), 7.2 (d, 1H), 7.7 (m, 2H), 7.9 (s, 1H), 8.0 (dd, 1H).

Example 13

This Example illustrates the preparation of (4-amino-3-methoxy-phenyl)-[4-(4-chloro-2-methyl-phenoxy)-[1,4']bipiperidinyl-1'-yl]-methanone ditrifluoroacetate (Compound 23 of Table IV).

A solution of the 4-(4-chloro-2-methyl-phenoxy)-piperidine (0.87mmol) and 1-(4-nitro-3-methoxy-benzoyl)-piperidin-4-one (0.925mmol) in NMP (5ml) and glacial acetic acid (1mmol) was stirred at RT for 1hour after which sodium triacetoxy borohydride (2mmol) was added. The resulting mixture was stirred at RT for 24hours, evaporated on to silica (2g) and placed on to a Mega Bond elut cartridge (10g Si). The product was eluted with DCM/MeOH mixtures and further purified by SCX, eluting the product with 10%aq NH_3 in MeOH. The nitro compound was dissolved in THF (10ml) and hydrogenated over 10%Pd on C at 3 atmospheres in Peteric apparatus. The mixture was filtered and the filtrate evaporated, the residue was then purified by RPHPLC, using a Symmetry column and

eluting with MeOH/ aqueous TFA mixtures. The product was isolated as the trifluoroacetate by evaporation of the appropriate HPLC fractions (0.046g; m.pt. 84-85°C).

^{1}H NMR (400MHz, DMSO-D6) δ 1.4-2.4 (m, 13H), 2.9 (m, 2H), 3.15 (m, 2H), 3.4 (m, 1H), 3.55 (m, 2H), 3.8 (s, 3H), 4.2 (bs, 2H), 4.55 and 4.8 (2bm, 1H), 6.68 (d, 1H), 6.82 (d, 1H), 6.85 (s, 1H), 7.0-7.22 (m, 2H), 7.25 (s, 1H), 9.5 (bm, 1H).

Example 14

This Example illustrates the preparation of 2-[1'-(3-methanesulfonyl-benzoyl)-[1,4']bipiperidinyl-4-yloxy]-5-trifluoromethyl-benzonitrile trifluoroacetate (Compound 291 of Table IV).

The product of Method E (183mg, 0.5mmol) was dissolved in DMSO (2ml) and treated with sodium hydride (22mg 1 equiv. of 60%) under an inert atmosphere. After stirring the mixture at RT for 1hour, 2-fluoro-5-trifluoromethyl-benzonitrile (1 equiv.) was added. After stirring at RT for 24 hours, the reaction mixture was acidified (glacial acetic acid) and filtered. The filtrate was purified by RPHPLC. (MeOH/aqueous TFA, Symmetry column) to give the product as the trifluoroacetate salt (0.06g; m.pt. 110-111°C).

^{1}H NMR (400MHz, DMSO-D6) δ 1.0-3.8 (m, 20 H), 4.5-5.3 (m, 2H), 7.5 (d, 1H), 7.75 (m, 3H), 8.02 (m, 2H).

Example 15

This Example illustrates the preparation of (3-methanesulfonyl-phenyl)-[4-(6-methyl-pyridin-2-yloxy)-[1,4']bipiperidinyl-1'-yl]-methanone trifluoroacetate (Compound 292 of Table IV).

The product of Method E (1mmol) and potassium tert-butoxide (2mmol) were stirred together in dry THF (20ml) at RT. After 10 mins 2-fluoro-6-methyl-pyridine (1mmol) was added and the reaction mixture stirred at reflux overnight. The reaction mixture was cooled, diluted with water and extracted into ethyl acetate (3x 50ml). The combined extracts were dried ($MgSO_4$) and evaporated. The residue was purified by RPHPLC. (MeOH/aqueous TFA, Symmetry column) to give the product as the trifluoroacetate salt (0.03g; m.pt. 61-62°C).

^{1}H NMR (400MHz, DMSO-D6) δ 1.6-3.8 (m, 15H), 2.4 (s, 3H), 3.3 (s, 3H), 4.5 - 5.4 (m, 3H), 6.6 (m, 1H), 6.02 (dd, 1H), 7.6 (q, 1H), 7.82 (m, 2H), 7.95 (s, 1H), 8.02 (m, 1H), 9.7 (bs, 1H)

Example 16

This Example illustrates the preparation of N-{3-[4-(3,4-dichloro-phenoxy)-[1,4']bipiperidinyl-1'-carbonyl]-phenyl}-methanesulfonamide (Compound 583 of Table I).

To (3-amino-phenyl)-[4-(3,4-dichloro-phenoxy)-[1,4']bipiperidinyl-1'-yl]-methanone (0.133g) in pyridine (2mL) was added methanesulfonyl chloride (0.024ml) and the reaction left to stir for 5 minutes. The solvent was evaporated, water (0.5mL) added and the solvent re-evaporated. Purification by RPHPLC (with a gradient eluent system (25% MeCN/NH_4OAc aq (0.1%) to 95% MeCN//NH_4OAc aq (0.1%)) gave the title compound (0.050g; m.pt. 94-95°C).

^1H NMR (399.978 MHz, $CDCl_3$) δ 1.59-2.09 (8H, m), 2.22 (2H, br s), 2.54-2.60 (1H, m), 2.81 (2H, br s), 3.02 (5H, br s), 3.51-3.75 (1H, br m), 4.25-4.28(1H, m), 4.29 (1H, br s), 6.70-7.52 (8H, m).

Example 17

This Example illustrates the preparation of N-{2-[4-(3,4-dichloro-phenoxy)-[1,4']bipiperidinyl-1'-carbonyl]-phenyl}-methanesulfonamide (Compound 587 of Table I).

To a solution of (2-amino-phenyl)-[4-(3,4-dichloro-phenoxy)-[1,4']bipiperidinyl-1'-yl]-methanone (0.2g) in pyridine (2ml) at 0°C was added methane sulphonyl chloride (0.039ml). The mixture was allowed to warm to room temperature and the pyridine removed by evaporation. The residue was azeotroped with water and the product purified by RPHPLC (Symmetry column, eluting 25% to 95% MeCN/0.1% NH_4OAc aq at 20ml/min over 6 minutes) to give the product as a colourless solid (0.09g).

^1H NMR: (399.978 MHz, $CDCl_3$) δ 1.49 - 1.69 (5H, m), 1.77 - 1.84 (2H, m), 1.87 - 1.94 (1H, m), 1.95 - 2.02 (2H, m), 2.43 - 2.50 (2H, m), 2.59 (1H, tt), 2.78 - 2.84 (2H, m), 2.87 - 3.03 (1H, m), 3.08 (3H, s), 3.17 (1H, sextet), 4.27 (1H, septet), 6.75 (1H, dd), 6.99 (1H, d), 7.15 (1H, td), 7.24 (1H, d), 7.31 (1H, d), 7.43 (1H, td), 7.62 (1H, d).

Example 18

This Example illustrates the preparation of [4-(3,4-dichloro-phenoxy)-[1,4']bipiperidinyl-1'-yl]-(1-methanesulfonyl-1H-indol-3-yl)-methanone hydrochloride (Compound 592 of Table I).

To a solution of Compound 471 of Table I (0.17g) in dimethylformamide (3ml) at 0°C under an atmosphere of nitrogen, was added sodium hydride (0.014g of a 60% suspension in oil). The mixture was stirred for 5 minutes then methanesulphonyl chloride (0.027ml in 1ml of dimethylformamide) was added and then mixture allowed to warm to

room temperature over 12 hours. The reaction mixture was partitioned between dichloromethane (10ml) and water (10ml). The organic layer was separated, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by RPHPLC (Symmetry, 25% to 95% MeCN/0.1% NH_4OAc aq over 6 minutes, 20ml/min, 220nm) to give a colourless solid (0.062g; m.pt. 173-175°C).

^1H NMR: (299.944 MHz DMSO-D6) δ 1.72 - 1.87 (2H, m), 2.01 - 2.34 (5H, m), 2.48 - 2.55 (1H, m), 2.98 - 3.13 (2H, m), 3.13 - 3.27 (2H, m), 3.39 - 3.47 (2H, m), 3.53 - 3.62 (2H, m), 3.64 (3H, s), 4.35 - 4.58 (1H, m), 4.65 - 4.76 (1H, m), 7.12 (1H, dd), 7.39 - 7.48 (2H, m), 7.52 (1H, t), 7.61 (1H, t), 7.79 (1H, d), 7.88 (1H, s), 7.95 (1H, d).

Example 19

This Example illustrates the preparation of 1-[4-(3,4-dichloro-phenoxy)-[1,4']bipiperidinyl-1'-yl]-2-phenyl-3-piperazin-1-yl-propan-1-one (Compound 595 of Table I).

Compound 575 of Table I (0.178g) was treated with 6N hydrochloric acid (5ml) and stirred at room temperature for 24hours. 2N Sodium hydroxide solution was added and the reaction mixture extracted with ethyl acetate. The organic extracts were combined, washed with water, dried ($MgSO_4$) and evaporated to give a white solid. Purification was by reverse phase HPLC (with a gradient eluent system (25% MeCN/NH_4OAc aq (0.1%) to 95% MeCN//NH4OAcaq (0.1%)). (Any excess NH_4OAc was removed by dissolving the compound in ethyl acetate and washing with aqueous saturated $NaHCO_3$ followed by drying of the organics with $MgSO_4$ and evaporation of solvent.) The title compound was a white solid (0.087g).

^1H NMR (399.98 MHz, DMSO-D6) δ 1.20 - 1.95 (9H, m), 2.10 - 2.53 (9H, m), 2.59 - 2.65 (2H, m), 2.70 - 2.77 (1H, m), 2.89 - 3.12 (4H, m), 4.02 - 4.47 (4H, m), 6.89 - 7.00 (1H, m), 7.16 - 7.32 (6H, m), 7.44 - 7.52 (1H, m).

Example 20

This Example illustrates the preparation of [4-(3,4-dichloro-phenoxy)-1-oxy-[1,4']bipiperidinyl-1'-yl]-(3-methanesulfonyl-phenyl)-methanone.

The product Example 10 (0.100g) in dichloromethane (5ml) was treated with m-chloroperbenzoic acid (0.043g) and the reaction stirred at room temperature for 0.5hours. Saturated aqueous sodium hydrogencarbonate was added and the reaction mixture extracted with dichloromethane. The combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated to give a brown foam. Purification by RPHPLC (with a

gradient eluent system (25% MeCN/NH_4OAc aq (0.1%) to 95% MeCN//NH_4OAc aq (0.1%)) gave the title compound as a white solid (0.021g).

^{1}H NMR (299.946 MHz, DMSO-D6) δ 1.70 - 2.91 (15H, m), 3.24 - 3.44 (3H, m), 3.55 - 3.68 (1H, m), 4.55 - 4.76 (2H, m), 6.99 - 7.06 (1H, m), 7.29 - 7.33 (1H, m), 7.53 (1H, dd), 7.71 - 7.79 (2H, m), 7.93 (1H, s), 7.99 - 8.05 (1H, m).

Example 21

This Example illustrates the preparation of [4-(3,4-dichloro-phenoxy)-[1,4']bipiperidinyl-1'-yl]-phenyl-methanone (Compound 1 of Table I).

To a solution of 4-(3,4-dichloro-phenoxy)-[1,4']bipiperidine (0.1g, see step b of Example 2) in dichloromethane (5ml) and triethylamine (0.2ml) was added benzoyl chloride (0.045ml) and the reaction mixture was stirred for 2hours. The mixture was washed with water, dried ($MgSO_4$), filtered and the solvents evaporated to leave a gum. Purification by RPHPLC [with an eluent system (50% MeCN/0.1%NH_4OAc aq), any excess NH_4OAc was removed by dissolving the compound in ethyl acetate and washing with aqueous saturated $NaHCO_3$ followed by drying of the organics with $MgSO_4$ and evaporation of solvent] and trituration of the resulting product with diethyl ether gave a solid which was filtered and dried to give the title compound (0.120g; m.pt. 122°C).

^{1}H NMR (299.944MHz $CDCl_3$) δ 1.42 - 1.62 (2H, m), 1.78 - 1.82 (3H, m), 1.95 - 2.01 (3H, m), 2.39 - 2.69 (3H, m), 2.69 - 3.09 (4H, m), 3.63 - 3.95 (1H, m), 4.24 - 4.29 (1H, m), 4.62 - 4.89 (1H, m), 6.73 - 6.77 (1H, m), 6.99 (1H, d), 7.26 - 7.29 (1H, m), 7.39 (5H, s).

Example 22

This Example illustrates the preparation of [4-(3,4-dichloro-benzenesulfonyl)-[1,4']bipiperidinyl-1'-yl]-(4-methanesulfonyl-phenyl)-methanone (Compound 4 of Table V).

Step 1: 4-(3,4-dichloro-phenylsulfanyl)-piperidine-1-carboxylic acid tert-butyl ester

4-Methanesulfonyloxy-piperidine-1-carboxylic acid tert-butyl ester (11.18g) and 3,4-dichlorothiophenol (6.15ml) were stirred together in acetonitrile (200ml) and potassium carbonate (8.86g) was added. The mixture was heated at reflux for 18hours after which water was added and the resulting mixture extracted with dichloromethane. The organic extracts were combined, washed with water, dried ($MgSO_4$) and evaporated to give the sub-title compound (14.58g).

^{1}H NMR (299.944MHz, $CDCl_3$) δ 1.45 (9H, s), 1.49 - 1.62 (2H, m), 1.87 - 1.96 (2H, m), 2.89 - 2.98 (2H, m), 3.16 - 3.26 (1H, m), 3.91 - 4.01 (2H, m), 7.21 - 7.57 (3H, m).

Step 2: 4-(3,4-dichloro-benzenesulfonyl)-piperidine-1-carboxylic acid tert-butyl ester

The product from Step 1 (1g) and m-chloroperbenzoic acid (1.19g) were stirred at ambient temperature in dichloromethane (10ml) for 18hours. Sodium metabisulphite (1.19g) in water (5ml) was added and stirring was continued for 0.5hours after which the reaction mixture was extracted with dichloromethane. The combined organics were washed with saturated sodium bicarbonate solution, dried ($MgSO_4$) and evaporated to give the sub-title compound (0.34g).

^{1}H NMR (399.978MHz, $CDCl_3$) δ 1.45 (9H, s), 1.56 - 1.65 (2H, m), 1.94 - 2.00 (2H, m), 2.62 - 2.70 (2H, m), 3.01 - 3.09 (1H, m), 4.21 - 4.30 (2H, m), 7.66 - 7.70 (2H, m), 7.93 - 7.98 (1H, m).

Step 3: 4-(3,4-dichloro-benzenesulfonyl)-piperidine

The product of step 2 was deprotected following the procedure of Example 1 step b. ^{1}H NMR (299.944 MHz, $CDCl_3$) δ 1.64 - 1.71 (2H, m), 1.96 - 2.05 (2H, m), 2.55 - 2.64 (2H, m), 2.99 - 3.10 (1H, m), 3.19 - 3.27 (2H, m), 7.66 - 7.71 (2H, m), 7.92 - 7.98 (1H, m).

Step 4: 4-(3,4-dichloro-benzenesulfonyl)-[1,4']bipiperidinyl-1'-carboxylic acid tert-butyl ester

The product of step 3 was used in a reductive amination with 4-oxo-piperidine-1-carboxylic acid tert-butyl ester following the procedure of Example 2 step a.

Step 5: 4-(3,4-Dichloro-benzenesulfonyl)-[1,4']bipiperidinyl

The product of step 4 was deprotected following the procedure of Example 2 step b. ^{1}H NMR (299.946 MHz, DMSO-D6) δ 1.22 - 1.61 (7H, m), 1.77 - 1.83 (2H, m), 2.09 - 2.16 (1H, m), 2.25 - 2.45 (3H, m), 2.87 - 2.98 (4H, m), 3.35 - 3.43 (1H, m), 7.81 (1H, dd), 7.96 (1H, d), 8.05 (1H, d)

Step 6: [4-(3,4-dichloro-benzenesulfonyl)-[1,4']bipiperidinyl-1'-yl]-(4-methanesulfonyl-phenyl)-methanone

The product of step 5 was coupled to 4-methanesulfonyl-benzoic acid following the procedure of Example 2 step c.

1H NMR (299.946 MHz, DMSO-D6) δ 1.34 - 1.62 (5H, m), 1.70 - 1.85 (4H, m), 2.13 (3H, t), 2.72 - 3.04 (4H, m), 3.27 (3H, s), 3.37 - 3.48 (1H, m), 4.44 - 4.52 (1H, m), 7.63 (2H, d), 7.81 (1H, dd), 7.95 - 8.00 (3H, m), 8.06 (1H, d).

[4-(3,4-Dichloro-benzenesulfonyl)-[1,4']bipiperidinyl-1'-yl]-phenyl-methanone (Compound 5 of Table V). The product of step 5 was coupled to benzoic acid following the procedure of Example 2 step c. ^{1}H NMR (299.946 MHz, DMSO-D6) δ 1.31 - 1.69 (5H, m), 1.82 (3H, d), 2.15 (2H, d), 2.69 - 2.75 (1H, m), 2.90 - 2.97 (4H, m), 3.33 - 3.43 (1H, m), 3.48 - 3.63 (1H, m), 4.42 - 4.53 (1H, m), 7.39 (5H, dt), 7.81 (1H, dd), 7.96 (1H, d), 8.06 (1H, d).

Example 23

This Example illustrates the preparation of 3-[4-(3,4-dichloro-phenoxy)-[1,4']bipiperidinyl-1'-carbonyl]-1-ethyl-7-methyl-1H-[1,8]naphthyridin-4-one (Compound 534 of Table I).

4-(3,4-Dichloro-phenoxy)-[1,4']bipiperidine (0.2g, see step b of Example 2) was dissolved in dichloromethane (5ml), bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PYBROP™; 0.425g), 1-ethyl-7-methyl-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid (0.155g) and triethylamine (0.254ml) were added. After 16 hours at room temperature dichloromethane and aqueous $NaHCO_3$ solution were added. The product was extracted with dichloromethane, the combined organic extracts were washed with water, dried with $MgSO_4$ and concentrated. Purification by RPHPLC (with a gradient eluent system (45% MeCN/NH_4OAc aq (0.1%) to 95% MeCN//NH_4OAc aq (0.1%)) %)) (any excess NH_4OAc was removed by dissolving the compound in ethyl acetate and washing with aqueous saturated $NaHCO_3$ followed by drying of the organics with Magnesium sulfate and evaporation of solvent) gave the title compound (0.184g; m.pt. 189-190°C)

MS: APCI$^+$(M+H) 543

^{1}H NMR (299.946 MHz, DMSO-D6) δ 1.37 (3H, t), 1.47- 1.69 (5H, m), 1.78-1.84 (1H, m), 1.89-1.97 (2H, m), 2.36 - 2.41 (2H, m), 2.49 - 2.56 (1H, m), 2.66 (3H, s), 2.70 - 2.79 (3H, m), 2.95 - 3.04 (1H, m), 3.52-3.59 (1H, m), 4.38-4.57 (4H, m), 6.95-6.99 (1H, m), 7.22-7.24 (1H, m), 7.35-7.40 (1H, m), 7.46-7.51 (1H, m), 8.37 (1H, s), 8.43-8.45 (1H, m).

Example 24

This Example illustrates the preparation of 4-[4-(3,4-dichloro-phenoxy)-[1,4']bipiperidinyl-1'-carbonyl]-2H-isoquinolin-1-one (Compound 572 of Table I).

4-(3,4-Dichloro-phenoxy)-[1,4']bipiperidine (0.2g, see step b of Example 2) was dissolved in dichloromethane (5ml), bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PYBROP™; 0.425g), 1-oxo-1,2-dihydro-isoquinoline-4-carboxylic acid (0.126g) and triethylamine (0.254ml) were added. After 16 hours at room temperature dichloromethane and aqueous $NaHCO_3$ solution were added. The product was extracted with dichloromethane, the combined organic extracts were washed with water, dried with $MgSO_4$ and concentrated. Purification by RPHPLC (with a gradient eluent system (45% MeCN/NH_4OAc aq (0.1%) to 95% MeCN//NH_4OAc aq (0.1%))) (any excess NH4OAc was removed by dissolving the compound in ethyl acetate and washing with aqueous saturated $NaHCO_3$ followed by drying of the organics with Magnesium sulfate and evaporation of solvent) gave the title compound (0.153g).

MS: APCI$^+$(M+H) 500

^{1}H NMR (299.944 MHz $CDCl_3$) δ 1.37 - 1.66 (2H, m), 1.73 - 1.88 (3H, m), 1.93 - 2.05 (3H, m), 2.41 - 2.51 (2H, m), 2.52 - 2.63 (1H, m), 2.75 - 2.86 (2H, m), 2.86 - 3.09 (2H, m), 3.71 - 3.90 (1H, m), 4.23 - 4.32 (1H, m), 4.77 - 4.93 (1H, m), 6.75 (1H, dd), 6.99 (1H, d), 7.27 - 7.32 (3H, m), 7.54 - 7.67 (1H, m), 7.57 (1H, t), 7.74 (1H, t), 8.46 (1H, d).

Example 25

This Example illustrates the preparation of [4-(3,4-dichloro-phenoxy)-[1,4']bipiperidinyl-1'-yl]-(6-fluoro-imidazo[1,2-a]pyridin-2-yl)-methanone (Compound 579 of Table I).

Step a: 6-Fluoro-imidazo[1,2-a]pyridine-2-carboxylic acid ethyl ester

To a solution of 2-amino-5-fluoropyridine (1.12g) in diethyl ether (25ml) was added ethyl bromopyruvate (1.25ml). the mixture was stirred for 1hour. The resultant solid was filtered off, suspended in ethanol and heated at reflux for 4hours. The solvent was removed by evaporation and the residue partitioned between ethyl acetate (100ml) and aqueous sodium bicarbonate solution (100ml). The organic layer was separated, dried, (magnesium sulfate) and the solvent removed by evaporation. The residue was purified by

flash chromatography (silica) eluting with ethyl acetate: hexane (3:1) to give the sub-title compound as a colourless solid (1.12g).

MS: ES^+(M+H) 209

^{1}H NMR (399.98 MHz, $CDCl_3$) δ 1.44 (3H, t), 4.46 (2H, q), 7.19 (1H, ddd), 7.68 (1H, dd), 8.07 - 8.09 (1H, m), 8.19 (1H, s).

Step b: 6-Fluoro-imidazo[1,2-a]pyridine-2-carboxylic acid

A solution of 6-fluoro-imidazo[1,2-a]pyridine-2-carboxylic acid ethyl ester (1g) in 4N HCl was refluxed for 4 hours. The solvent was evaporated to give the sub-title compound as a white solid (0.86g).

MS: ES^+(M+H) 181

^{1}H NMR (399.98 MHz, DMSO-D6) δ 7.81 - 7.89 (2H,m), 8.71 (1H,s), 9.03 (1H,s).

Step c: [4-(3,4-Dichloro-phenoxy)-[1,4']bipiperidinyl-1'-yl]-(6-fluoro-imidazo[1,2-a]pyridin-2-yl)-methanone

4-(3,4-Dichloro-phenoxy)-[1,4']bipiperidine (0.2g, see step b of Example 2) was dissolved in dichloromethane (5ml), bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PYBROP™; 0.425g), 6-fluoro-imidazo[1,2-a]pyridine-2-carboxylic acid (0.126g) and triethylamine (0.254ml) were added. After 16 hours at room temperature dichloromethane and aqueous $NaHCO_3$ solution were added. The product was extracted with dichloromethane, the combined organic extracts were washed with water, dried with $MgSO_4$ and concentrated. Purification by reverse phase HPLC (with a gradient eluent system (45% MeCN/NH_4OAc aq (0.1%) to 95% MeCN//NH_4OAc aq (0.1%)) (any excess NH_4OAc was removed by dissolving the compound in ethyl acetate and washing with aqueous saturated $NaHCO_3$ followed by drying of the organics with magnesium sulfate and evaporation of solvent) gave the title compound (0.104g).

MS: $APCI^+$(M+H) 491

^{1}H NMR (399.978MHz,$CDCl_3$) δ 1.61 (1H, qd), 1.75 - 2.02 (7H, m), 2.42 - 2.51 (2H, m), 2.59 - 2.67 (1H, m), 2.75 - 2.86 (3H, m), 3.12 - 3.21 (1H, m), 4.23 - 4.29 (1H, m), 4.76 - 4.85 (1H, m), 5.23 - 5.32 (1H, m), 6.75 (1H, dd), 6.99 (1H, d), 7.16 (1H, ddd), 7.30 (1H, d), 7.58 (1H, dd), 8.07 (2H, s).

Example 26

This Example illustrates the preparation of 4-(3,4-dichloro-phenoxy)-[1,4']bipiperidinyl-1'-carboxylic acid phenylamide (Compound 309 of Table IV).

Phenylisocyanate(0.078ml) was added to a solution of 4-(3,4-dichloro-phenoxy)-[1,4']bipiperidine (0.2g, see Example 2 step b) in dichloromethane (5ml). The mixture was stirred at 23°C for 16hours. The resulting precipitate was filtered, washed with dichloromethane (2 x 5ml) then crystallised from acetonitrile to afford the title compound as a solid (0.2g; melting point 215-216°C).

^{1}H NMR (DMSO-D6) δ 1.35 (2H, qd), 1.53 - 1.62 (2H, m), 1.72 - 1.78 (2H, m), 1.89 - 1.96 (2H, m), 2.36 - 2.42 (2H, m), 2.44 - 2.52 (1H, m), 2.72 - 2.78 (4H, m), 4.15 (2H, d), 4.39 - 4.45 (1H, m), 6.91 (1H, tt), 6.98 (1H, dd), 7.19 - 7.23 (2H, m), 7.25 (1H, d), 7.43 - 7.46 (2H, m), 7.49 (1H, d), 8.46 (1H, s).

4-(3,4-Dichloro-phenoxy)-[1,4']bipiperidinyl-1'-carbothioic acid phenylamide was prepared using the methodology of Example 26 and employing phenylisothiocyanate, (melting point 162-163°C). ^{1}H NMR: (DMSO-d6) δ 1.39 - 1.49 (2H, m), 1.53 - 1.62 (2H, m), 1.79 (2H, d), 1.89 - 1.96 (2H, m), 2.39 (2H, t), 2.54 - 2.63 (1H, m), 2.73 - 2.80 (2H, m), 3.04 (2H, t), 4.39 - 4.46 (1H, m), 4.72 (2H, d), 6.98 (1H, dd), 7.06 - 7.10 (1H, m), 7.23 - 7.30 (5H, m), 7.49 (1H, d), 9.24 (1H, s).

Example 27

This Example illustrates the preparation of 4-(3,4-dichloro-phenoxy)-[1,4']bipiperidinyl-1'-carboxylic acid (3-methanesulfonyl-phenyl)-amide (Compound 54 of Table IV).

Hydrogen peroxide (100µl, 30%) was added to a cooled (0°C) solution of Compound 312 of Table IV (0.13g) in trifluoroacetic acid(1ml). The mixture was allowed to reach ambient temperature and stirred for a further 1hour. The solution was quenched with water(5ml), basified to pH11 with 2M sodium hydroxide solution and extracted with ethyl acetate. The organic solution was separated, washed with water(2x5ml), dried ($MgSO_4$), filtered and the filtrate evaporated to leave a gum. The gum was dissolved in acetonitrile and purified by RPHPLC (Nova Pak column) eluting with acetonitrile/ 0.1% ammonium acetate aq (1:1). The required fractions were evaporated and then lyophilised to give the title compund as a colourless powder (0.03g).

^{1}H NMR (DMSO-D6) δ 1.31 - 1.42 (2H, m), 1.53 - 1.62 (2H, m), 1.77 (2H, d), 1.89 - 1.96 (2H, m), 2.36 - 2.43 (3H, m), 2.74 - 2.82 (4H, m), 3.16 (3H, s), 4.18 (2H, d), 4.42 (1H, septet), 6.98 (1H, dd), 7.25 (1H, d), 7.44 - 7.52 (3H, m), 7.80 - 7.83 (1H, m), 8.09 (1H, t), 8.90 (1H, s).

Selected proton NMR data and/or melting point data are provided for certain further compounds in Tables VI and VII below.

TABLE VI

Compound (Table no.)	NMR data
3 (I)	δ(D_2O) 1.97 – 1.69 (2H, m), 2.21 – 2.08 (2H, m), 2.51 – 2.23 (4H, m), 3.07 – 2.96 (1H, m), 3.31 – 3.17 (2H, m), 3.45 – 3.32 (2H, m), 3.56 – 3.45 (1H, m), 3.75 – 3.56 (2H, m), 4.88 – 4.70 (3H, m), 7.07 – 7.02 (1H, m), 7.36 – 7.30 (1H, m), 7.46 – 7.37 (1H, m), 7.55 (2H, d), 7.74 – 7.72 (1H, m)
8 (I)	δ($CDCl_3$) 1.67 – 1.41 (2H, m), 1.86 – 1.76 (3H, m), 2.04 – 1.93 (3H, m), 2.51 – 2.42 (3H, m), 2.62 – 2.56 (1H, m), 2.88 – 2.76 (3H, m), 3.06 (1H, t), 3.66 (1H, d), 4.28 (1H, septet), 4.76 (1H, d), 6.75 (1H, dd), 6.99 (1H, d), 7.31 (1H, d), 7.56 (2H, d), 8.28 (2H, d)
18 (I)	δ(CD_3OD) 1.59 – 1.41 (2H, m), 1.83 – 1.68 (2H, m), 2.08 – 1.93 (4H, m), 2.56 – 2.48 (4H, m), 2.68 – 2.61 (1H, m), 2.91 – 2.80 (3H, m), 3.15 – 3.02 (1H, m), 3.71 – 3.57 (1H, m), 4.23 – 4.14 (1H, m), 4.40 (1H, septet), 4.50 (3H, s), 4.75 – 4.57 (1H, m), 6.91 (1H, dd), 7.12 (1H, d), 7.40 (1H, d), 7.66 (2H, d), 8.04 (2H, d)
36 (I)	δ(CD_3OD) 1.62 – 1.42 (2H, m), 1.94 – 1.72 (3H, m), 2.11 – 1.98 (3H, m), 2.61 – 2.52 (2H, m), 2.95 – 2.82 (3H, m), 3.15 (1H, t), 3.68 – 3.63 (1H, m), 4.42 (1H, septet), 4.71 – 4.67 (2H, m), 6.91 (1H, dd), 7.11 (1H, d), 7.40 (1H, d), 7.60 (2H, d), 7.86 (2H, d)
37 (I)	δ(CD_3OD) 2.06 – 1.76 (3H, m), 2.45 – 2.12 (5H, m), 3.05 – 2.88 (1H, m), 3.42 – 3.25 (3H, m), 3.71 – 3.50 (2H, m), 3.93 – 3.74 (1H, m), 4.63 (1H, septet), 4.94 – 4.82 (2H, m), 7.03 – 6.95 (1H, m), 7.24 (1H, dd), 7.47 – 7.42 (1H, m), 7.71 – 7.66 (1H, m), 7.78 (1H, td), 7.90 – 7.86 (2H, m)

149 (I)	δ($CDCl_3$) 1.50 – 1.27 (2H, m), 1.90 – 1.75 (5H, m), 2.02 – 1.92 (2H, m), 2.56 – 2.39 (4H, m), 2.63 (1H, t), 2.81 – 2.72 (2H, m), 3.09 – 3.01 (3H, m), 3.82 (2H, s), 3.91 (1H, d), 4.25 (1H, septet), 4.67 (1H, d), 6.75 (1H, dd), 6.99 (1H, d), 7.31 (1H, dd), 7.45 (2H, d), 7.90 (2H, d)
203 (I)	δ(DMSO-D6) 1.61 – 1.44 (2H, m), 2.24 – 2.01 (4H, m), 2.61 – 2.53 (2H, m), 3.16 – 2.99 (2H, m), 3.60 – 3.30 (5H, m), 3.67 (2H, s), 3.77 (3H, s), 4.13 (1H, d), 4.53 (1H, d), 4.69 – 4.60 (1H, m), 7.05 (1H, ddd), 7.14 (1H, d), 7.42 – 7.25 (3H, m), 7.55 (2H, dd), 10.98 – 10.78 (3H, m)
205 (I)	δ($(CD_3)_2CO$) 1.26 (2H, quintet), 1.76 – 1.58 (4H, m), 1.98 – 1.90 (2H, m), 2.42 – 2.35 (2H, m), 2.58 – 2.45 (2H, m), 2.81 – 2.71 (2H, m), 3.00 (1H, t), 3.70 (2H, s), 4.00 (1H, d), 4.39 (2H, septet), 4.51 (1H, d), 6.92 (1H, dd), 7.07 – 7.01 (2H, m), 7.13 (1H, d), 7.30 – 7.25 (2H, m), 7.40 (1H, d)
220 (I)	δ(DMSO-D6) 1.58 – 1.44 (2H, m), 2.28 – 1.97 (5H, m), 2.59 – 2.53 (2H, m), 3.18 – 2.93 (3H, m), 3.34 – 3.25 (1H, m), 3.51 – 3.36 (2H, m), 3.66 – 3.56 (2H, m), 4.11 (1H, d), 4.53 (1H, d), 4.64 (1H, septet), 6.92 – 6.82 (2H, m), 6.99 (1H, d), 7.10 – 7.03 (1H, m), 7.36 (1H, dd), 7.55 (1H, ddd), 10.99 – 10.87 (1H, m)
225 (I)	δ($(CD_3)_2CO$) 1.71 – 1.51 (2H, m), 2.13 – 2.08 (2H, m), 2.40 – 2.21 (3H, m), 2.61 – 2.54 (1H, m), 3.05 (1H, t), 3.55 – 3.15 (6H, m), 3.69 – 3.61 (2H, m), 4.16 (1H, d), 4.76 – 4.63 (2H, m), 4.91 – 4.86 (1H, m), 6.78 – 6.76 (2H, m), 7.12 – 7.02 (3H, m), 7.32 (1H, dd), 7.51 (1H, dd)
244 (I)	δ(DMSO-D6) 1.55 – 1.42 (2H, m), 2.25 – 1.96 (6H, m), 2.66 – 2.54 (2H, m), 3.14 – 2.96 (2H, m), 3.32 – 3.26 (1H, m), 3.51 – 3.35 (2H, m), 3.62 (3H, s), 3.71 – 3.64 (2H, m), 3.74 (6H, s), 4.14 (1H, d), 4.54 (1H, d), 4.66 – 4.58 (1H, m), 6.53 (2H, s), 7.04 (1H, dd), 7.35 (1H, d), 7.54 (1H, tt)
253 (I)	δ($CDCl_3$) 1.47 – 1.19 (2H, m), 2.00 – 1.76 (6H, m), 2.62 – 2.37 (4H, m), 2.80 – 2.70 (2H, m), 2.98 (1H, t), 3.65 (2H, s), 3.88 (3H, s), 3.92 – 3.89 (1H, m), 4.25 (1H, septet), 4.68 (1H, d), 6.77 – 6.72 (1H, m), 6.89 (1H, d), 6.94 – 6.92 (2H, m), 7.01 – 6.96 (2H, m), 7.30 (1H, dd)
258 (I)	δ(DMSO-D6) 1.40 – 1.26 (3H, m), 1.78 – 1.59 (5H, m), 1.98 – 1.92 (1H, m), 2.17 (3H, s), 2.21 (3H, s), 2.45 – 2.37 (2H, m), 2.60- 2.48 (3H, m), 3.01 (1H, t), 3.70- 3.57 (2H, m), 3.89 (1H, d), 4.39 (1H, septet), 4.55 (1H,

	d), 7.00 (1H, d), 7.13 (1H, d), 7.41 (1H, d), 7.95- 7.89 (3H, m)
267 (I)	δ($CDCl_3$) 1.74 – 1.61 (2H, m), 2.21 – 2.09 (3H, m), 2.32 – 2.25 (1H, m), 2.48 (1H, t), 2.67 – 2.53 (2H, m), 2.89 (1H, t), 3.31 – 3.05 (5H, m), 3.71 (4H, s), 3.82 (2H, s), 4.08 (1H, d), 4.59 – 4.53 (1H, m), 4.94 (1H, d), 6.89 (1H, dd), 6.93 (1H, dd), 6.97 (1H, d), 7.34 (1H, d), 7.40 (1H, d), 7.58 – 7.54 (1H, m),
268 (I)	δ($CDCl_3$) 1.24 (1H, dq), 1.41 (1H, dq), 1.88 – 1.72 (4H, m), 2.00 – 1.91 (2H, m), 2.53 – 2.37 (3H, m), 2.59 (1H, dt), 2.78 – 2.70 (2H, m), 2.98 (1H, t), 3.73 (2H, s), 3.89 (1H, d), 4.24 (1H, septet), 4.68 (1H, d), 6.74 (1H, dd), 7.03 – 6.91 (4H, m), 7.29 – 7.25 (1H, m), 7.30 (1H, d)
272 (I)	δ($CDCl_3$) 1.18 (1H, dq), 1.40 (1H, dq), 1.86 – 1.68 (4H, m), 2.00 – 1.91 (2H, m), 2.43 – 2.35 (2H, m), 2.48 (1H, td), 2.57 (1H, dt), 2.77 – 2.68 (2H, m), 2.95 (1H, dt), 3.74 (2H, s), 3.91 (1H, d), 4.23 (1H, septet), 4.69 (1H, d), 6.74 (1H, dd), 6.98 (1H, d), 7.35 – 7.23 (6H, m)
274 (I)	δ(DMSO-D6) 1.74- 1.59 (5H, m), 1.77 (3H, dq), 2.65- 2.36 (4H, m), 2.86 – 2.74 (6H, m), 2.95 (1H, t), 3.74 (3H, s), 3.93 (1H, d), 4.40 (1H, septet), 4.53 (1H, d), 6.73 – 6.70 (1H, m), 6.80- 6.78 (2H, m), 6.93 (1H, dd), 7.18 – 7.13 (2H, m), 7.41 (1H, d)
276 (I)	δ($(CD_3)_2CO$) 1.63 – 1.51 (2H, m), 2.02 – 1.98 (2H, m), 2.21 – 2.15 (2H, m), 2.58 – 2.31 (4H, m), 2.96 (1H, t), 3.40 – 3.03 (4H, m), 3.60 – 3.49 (2H, m), 3.72 (3H, s), 4.02 (1H, d), 4.63 – 4.55 (1H, m), 4.77 – 4.72 (1H, m), 6.76 (1H, t), 6.84 (1H, d), 6.96 – 6.93 (1H, m), 7.03 (1H, d), 7.11 – 7.07 (1H, m), 7.16 – 7.15 (1H, m), 7.37 – 7.31 (1H, m)
286 (I)	δ(CD_3OD) 1.90 – 1.63 (2H, m), 2.49 – 2.05 (6H, m), 3.28 – 2.87 (7H, m), 3.84 – 3.44 (5H, m), 4.69 – 4.56 (1H, m), 4.85 – 4.78 (2H, m), 7.04 – 6.94 (1H, m), 7.28 – 7.21 (1H, m), 7.45 (1H, t), 7.60 – 7.55 (3H, m), 7.64 – 7.61 (1H, m), 7.66 (1H, t), 7.77 – 7.73 (2H, m), 7.85 – 7.81 (2H, m)
291 (I)	δ(CD_3OD) 1.98 – 1.71 (3H, m), 2.46 – 2.11 (5H, m), 3.18 – 2.98 (1H, m), 3.45 – 3.26 (2H, m), 3.70 – 3.46 (4H, m), 3.86 (3H, s), 4.66 – 4.56 (1H, m), 4.84 – 4.80 (2H, m), 7.04 – 6.94 (3H, m), 7.27 – 7.20 (1H, m), 7.47 – 7.42 (3H, m)
293 (I)	δ(CD_3OD) 1.88 – 1.73 (2H, m), 2.22 – 1.92 (5H, m), 2.31 (1H, d), 2.87 –

	2.79 (1H, m), 3.06 – 2.97 (1H, m), 3.17 (3H, s), 3.57 – 3.31 (5H, m), 4.55 – – 4.44 (1H, m), 4.73 – 4.65 (2H, m), 6.92 – 6.82 (1H, m), 7.12 (1H, td), 7.40 – 7.31 (2H, m), 7.63 (1H, dt), 7.75 – 7.68 (1H, m), 7.99 (1H, dt)
294 (I)	δ(CD_3OD) 1.98 – 1.70 (2H, m), 2.45 – 2.08 (6H, m), 2.97 (1H, t), 3.21 (3H, s), 3.41 – 3.21 (3H, m), 3.72 – 3.49 (3H, m), 4.67 – 4.56 (1H, m), 4.95 – 4.81 (2H, m), 7.03 – 6.94 (1H, m), 7.27 – 7.20 (1H, m), 7.47 – 7.42 (1H, m), 7.74 – 7.62 (1H, m), 8.02 (1H, ddd), 8.13 (1H, dd)
295 (I)	δ(CD_3OD) 2.04 – 1.74 (3H, m), 2.36 – 2.12 (4H, m), 2.48 – 2.40 (1H, m), 3.03 – 2.87 (1H, m), 3.43 – 3.15 (3H, m), 3.80 – 3.47 (3H, m), 4.68 – 4.58 (1H, m), 4.85 – 4.80 (2H, m), 5.13 (2H, s), 7.03 – 6.96 (1H, m), 7.27 – 7.21 (1H, m), 7.46 – 7.42 (1H, m), 7.63 – 7.56 (3H, m), 7.79 – 7.69 (4H, m), 8.12 (1H, d)
296 (I)	δ(CD_3OD) 2.46 – 1.75 (8H, m), 2.96 (1H, t), 3.32 (2H, s), 3.72 – 3.19 (4H, m), 3.97 – 3.92 (1H, m), 4.69 – 4.56 (1H, m), 4.98 – 4.79 (2H, m), 7.03 – 6.94 (1H, m), 7.24 (1H, d), 7.69 – 7.35 (10H, m)
297 (I)	δ(CD_3OD) 1.66 – 1.51 (2H, m), 1.89 – 1.69 (3H, m), 2.08 – 1.96 (3H, m), 2.71 – 2.50 (3H, m), 3.01 – 2.81 (3H, m), 3.24 – 3.10 (1H, m), 3.84 – 3.71 (1H, m), 4.46 – 4.38 (1H, m), 4.79 – 4.67 (1H, m), 6.92 (1H, dd), 7.14 (1H, d), 7.41 (1H, d), 7.81 (1H, dd), 8.39 (1H, d), 8.71 (1H, s)
298 (I)	δ(CD_3OD) 1.33 (3H, t), 1.62 – 1.41 (2H, m), 1.95 – 1.74 (3H, m), 2.11 – 1.98 (3H, m), 2.73 – 2.52 (3H, m), 2.95 – 2.79 (3H, m), 3.03 (2H, q), 3.26 – 3.09 (1H, m), 3.93 – 3.78 (1H, m), 4.48 – 4.39 (1H, m), 4.78 – 4.56 (1H, m), 6.91 (1H, dd), 7.11 (1H, d), 7.42 – 7.34 (5H, m)
299 (I)	δ(CD_3OD) 1.99 – 1.72 (3H, m), 2.36 – 2.11 (4H, m), 2.44 (1H, d), 3.06 – 2.87 (1H, m), 3.42 – 3.23 (2H, m), 3.71 – 3.46 (4H, m), 3.95 – 3.77 (1H, m), 4.67 – 4.55 (1H, m), 4.84 – 4.80 (1H, m), 7.03 – 6.94 (1H, m), 7.27 – 7.20 (1H, m), 7.47 – 7.43 (1H, m), 7.66 – 7.61 (2H, m), 7.87 – 7.81 (2H, m)
300 (I)	δ(CD_3OD) 1.96 – 1.72 (3H, m), 2.33 – 2.09 (4H, m), 2.46 – 2.41 (1H, m), 3.02 – 2.87 (1H, m), 3.43 – 3.22 (3H, m), 3.72 – 3.47 (3H, m), 3.93 – 3.78 (1H, m), 4.66 – 4.56 (1H, m), 4.84 – 4.80 (1H, m), 7.03 – 6.94 (1H, m), 7.28 – 7.21 (1H, m), 7.47 – 7.43 (1H, m), 7.59 (2H, d), 7.83 (2H, d)

301 (I)	(500.076 MHz, DMSO-D6) δ 1.33-1.44 (m, 2H), 1.55-1.60 (m, 2H), 1.66-1.73 (m, 1H), 1.78-1.86 (m, 1H), 1.91 (s, 3H), 1.91-1.96 (m, 2H), 2.05 (s, 3H), 2.39 (t, 2H), 2.55 (t, 1H), 2.74-2.79 (m, 3H), 2.94-3.04 (m, 1H), 3.56-3.66 (m, 1H), 4.42 (septet, 1H), 4.45-4.52 (m, 1H), 6.98 (dd, 2H), 7.02 (d, 2H), 7.25 (d, 1H), 7.35 (t, 1H), 7.49 (d, 1H), 7.58 (d, 1H), 7.66 (s, 1H)
302 (I)	(500.076 MHz, DMSO-D6) δ 1.36 (dq, 2H), 1.54 – 1.60 (m, 2H), 1.72 – 1.75 (m, 2H), 1.91 (s, 3H), 1.91 – 1.95 (m, 2H), 2.05 (s, 3H), 2.39 (t, 2H), 2.74 – 2.78 (m, 2H), 2.80 – 2.87 (m, 1H), 4.05 – 4.19 (m, 2H), 4.42 (septet, 1H), 5.22 (s, 2H), 6.58 (d, 1H), 6.97 – 6.99 (m, 2H), 7.00 (s,1H), 7.25 (d, 1H), 7.49 (d, 1H)
303 (I)	(500.076 MHz, DMSO-D6) δ 1.54 – 1.63 (m, 4H), 1.69 – 1.82 (m, 4H), 1.91 – 1.96 (m, 2H), 1.91 (s, 3H), 2.35 – 2.44 (m, 2H), 2.73 – 3.04 (m, 7H), 4.39 – 4.46 (m, 2H), 6.48 – 6.49 (m, 1H), 6.98 (d, 1H), 7.02 – 7.07 (m, 3H), 7.26 (s, 1H), 7.34 (t, 1H), 7.49 (d, 1H), 7.62 (d, 1H)
304 (I)	(500.076 MHz, DMSO-D6) δ 1.33 (t, 3H), 1.36 – 1.43 (m, 2H), 1.54 – 1.60 (m, 2H), 1.70 – 1.80 (m, 2H), 1.91 – 1.96 (m, 2H), 1.91 (s, 3H), 2.39 (t, 2H), 2.51 – 2.55 (m, 1H), 2.74 – 2.79 (m, 2H), 3.79 (s, 3H), 4.01 – 4.05 (m, 1H), 4.02 (q, 2H), 4.42 (septet, 1H), 4.47 – 4.53 (m, 1H), 6.94 (s, 2H), 6.97 – 6.99 (m, 2H), 7.25 (d, 1H), 7.49 (d, 1H)
305 (I)	(500.076 MHz, DMSO-D6) δ 1.37 – 1.46 (m, 2H), 1.54 – 1.61 (m, 2H), 1.67 – 1.83 (m, 2H), 1.91 – 1.96 (m, 2H), 1.91 (s, 3H), 2.40 (t, 2H), 2.53 – 2.58 (m, 1H), 2.74 – 2.80 (m, 2H), 2.99 – 3.10 (m, 1H), 3.63 – 3.74 (m, 1H), 4.42 (septet, 1H), 4.46 – 4.54 (m, 1H), 6.29 – 6.30 (m, 1H), 6.98 (dd, 1H), 7.25 (d, 1H), 7.43 – 7.44 (m, 1H), 7.48 (t, 3H), 7.64 (d, 2H)
306 (I)	(500.076 MHz, DMSO-D6) δ 1.22 – 1.40 (m, 2H), 1.54 – 1.61 (m, 2H), 1.75 (t, 2H), 1.91 – 1.96 (m, 2H), 2.38 (t, 2H), 2.53 – 2.60 (m, 1H), 2.71 – 2.77 (m, 2H), 3.03 (t, 1H), 3.79 (s, 2H), 3.98 – 4.03 (m, 1H), 4.36 – 4.40 (m, 1H), 4.40 – 4.45 (m, 1H), 6.98 (dd, 1H), 7.25 (d, 1H), 7.50 (d, 1H), 8.34 (s, 1H), 8.40 (s, 1H), 8.57 (d, 1H)
307 (I)	(500.076 MHz, DMSO-D6) δ 1.17 – 1.31 (m, 2H), 1.53 – 1.59 (m, 2H), 1.69 (t, 2H), 1.88 – 1.94 (m, 2H), 2.35 (t, 2H), 2.45 – 2.52 (m, 1H), 2.68 –

	2.74 (m, 2H), 2.95 (t,1H), 3.50 (s,2H), 3.59 (s,3H), 4.06 – 4.10 (m,1H), 4.36 – 4.43 (m,2H), 6.88 (s,1H), 6.97 (dd,1H), 7.25 (d,1H), 7.45 (s,1H), 7.49 (d,1H)
308 (I)	(500.076 MHz, DMSO-D6) δ 1.03 (dq, 1H), 1.18 (dq, 1H), 1.49 – 1.58 (m, 3H), 1.68 (d, 1H), 1.83 – 1.90 (m, 2H), 1.91 (s, 3H), 2.23 – 2.30 (m, 2H), 2.41 – 2.49 (m, 3H), 2.57 – 2.67 (m, 2H), 2.90 (t, 1H), 3.66 (q, 2H), 4.01 (d, 1H), 4.38 (septet, 1H), 4.43 (d, 1H), 6.58 (dd, 1H), 6.88 (d, 1H), 6.96 (dd, 1H), 7.07 (d, 1H), 7.12 (d, 1H), 7.23 (d, 1H), 7.49 (d, 1H), 8.58 (s, 1H)
309 (I)	(500.076 MHz, DMSO-D6) δ 1.46 – 1.56 (m, 2H), 1.89 – 1.98 (m, 2H), 2.03 – 2.18 (m, 4H), 2.23 (d, 1H), 2.55 – 2.61 (m, 1H), 3.02 – 3.17 (m, 4H), 3.42 – 3.51 (m, 2H), 3.98 (s, 2H), 4.16 (d, 1H), 4.54 (d, 1H), 4.60 – 4.66 (m, 1H), 6.93 – 6.97 (m, 1H), 7.01 – 7.09 (m, 1H), 7.15 (s, 1H), 7.25 (s, 1H), 7.34 – 7.38 (m, 1H), 7.54 – 7.58 (m, 1H)
310 (I)	(500.076 MHz, DMSO-D6) δ 1.11 (t, 3H), 1.39 – 1.48 (m, 2H), 1.55 – 1.60 (m, 2H), 1.65 – 1.72 (m, 1H), 1.81 – 1.87 (m, 1H), 1.90 – 1.95 (m, 2H), 1.90 (s, 3H), 2.39 (t, 2H), 2.53 – 2.59 (m, 1H), 2.74 – 2.83 (m, 2H), 3.03 – 3.10 (m, 1H), 3.36 (q, 2H), 3.47 – 3.55 (m, 1H), 4.42 (septet, 1H), 4.46 – 4.54 (m, 1H), 6.98 (dd, 1H), 7.25 (d, 1H), 7.49 (d, 1H), 7.72 – 7.78 (m, 2H), 7.86 (s, 1H), 7.96 (d, 1H)
311 (I)	(500.076 MHz, DMSO-D6) δ 0.92 (t, 3H), 1.40 – 1.49 (m, 2H), 1.55 – 1.64 (m, 2H), 1.57 (sextet, 2H), 1.65 – 1.73 (m, 1H), 1.81 – 1.88 (m, 1H), 1.91 (s, 3H), 1.91 – 1.96 (m, 2H), 2.36 – 2.44 (m, 2H), 2.54 – 2.61 (m, 1H), 2.73 – 2.84 (m, 2H), 3.02 – 3.11 (m, 1H), 3.45 – 3.53 (m, 1H), 4.40 – 4.46 (m, 1H), 4.50 – 4.54 (m, 1H), 6.98 (dd, 1H), 7.25 (d, 1H), 7.49 (d, 1H), 7.72 – 7.78 (m, 2H), 7.86 (s, 1H), 7.96 (d, 1H)
312 (I)	(500.076 MHz, DMSO-D6) δ 0.98 (d, 6H), 1.39 – 1.49 (m, 2H), 1.54 – 1.61 (m, 2H), 1.64 – 1.71 (m, 1H), 1.81 – 1.87 (m, 1H), 1.90 – 1.95 (m, 2H), 1.91 (s, 3H), 2.02 (septet, 1H), 2.39 (t, 2H), 2.53 – 2.59 (m, 1H), 2.74 – 2.79 (m, 2H), 3.03 – 3.11 (m, 1H), 3.45 – 3.52 (m, 1H), 4.42 (septet, 1H), 4.47 – 4.53 (m, 1H), 6.98 (dd, 1H), 7.25 (d, 1H), 7.49 (d, 1H), 7.71 – 7.77 (m, 2H), 7.88 (s, 1H), 7.98 (d, 1H)

313 (I)	(500.076 MHz, DMSO-D6) δ 1.41 – 1.53 (m, 2H), 1.54 – 1.62 (m, 2H), 1.66 – 1.74 (m, 1H), 1.84 – 1.89 (m, 1H), 1.91 – 1.96 (m, 2H), 1.91 (s, 3H), 2.36 – 2.44 (m, 2H), 2.54 – 2.62 (m, 1H), 2.73 – 2.87 (m, 4H), 3.10 (t, 1H), 3.50 (s, 3H), 3.52 (s, 3H), 3.52 – 3.58 (m, 1H), 4.40 – 4.46 (m, 1H), 4.48 – 4.54 (m, 1H), 6.97 – 7.00 (m, 1H), 7.23 – 7.29 (m, 1H), 7.50 (d, 1H), 8.06 (d, 1H), 8.16 (s, 1H), 8.29 (d, 1H)
314 (I)	(500.076 MHz, DMSO-D6) δ 1.34 (t, 3H), 1.35 – 1.41 (m, 2H), 1.54 – 1.60 (m, 2H), 1.74 (d, 2H), 1.90 – 1.96 (m, 2H), 1.90 (s, 3H), 2.39 (t, 2H), 2.50 – 2.55 (m, 1H), 2.73 – 2.79 (m, 2H), 2.80 – 2.89 (m, 1H), 4.01 (q, 2H), 4.08 – 4.19 (m, 2H), 4.42 (septet, 2H), 5.06 (s, 2H), 6.62 (d, 1H), 6.77 (d, 1H), 6.81 (s, 2H), 6.98 (dd, 1H), 7.25 (d, 1H), 7.49 (d, 1H)
315 (I)	(DMSO-D6) δ 1.53 – 1.82 (m, 2H), 2.02 – 2.36 (m, 5H), 2.60 – 2.67 (m, 1H), 3.07 – 3.15 (m, 2H), 3.31 – 3.38 (m, 1H), 3.43 – 3.53 (m, 2H), 4.12 – 4.19 (m, 4H), 4.51 (d, 1H), 4.68 (septet, 1H), 4.85 (s, 1H), 7.06 (ddd, 1H), 7.37 (dd, 1H), 7.56 (t, 1H), 7.94 (d, 2H), 8.86 (d, 2H), 11.47 (s, 1H)
316 (I)	(DMSO-D6) δ 1.58 – 2.28 (m, 4H), 2.67 – 2.84 (m, 1H), 2.91 – 3.04 (m, 2H), 2.97 (s, 2H), 3.06 – 3.26 (m, 2H), 3.24 – 3.42 (m, 1H), 3.44 – 3.67 (m, 3H), 3.57 (s, 3H), 4.55- 4.77 (m,2H), 4.83 (s,1H), 7.00- 7.09 (m,2H), 7.35- 7.58 (m, 5H)
317 (I)	(DMSO-D6) δ 1.52 (dq, 2H), 1.74 – 1.92 (m, 2H), 1.93 – 2.04 (m, 4H), 2.42 – 2.50 (m, 2H), 2.55 (tt, 1H), 2.77 – 2.85 (m, 2H), 2.87 – 2.96 (m, 2H), 4.22 – 4.30 (m, 3H), 6.69 – 6.74 (m, 2H), 6.76 (d, 1H), 6.99 (d, 1H), 7.07 (dd, 1H), 7.16 (dt, 1H), 7.29 (s, 2H), 7.32 (s, 1H)
318 (I)	(DMSO-D6) δ 1.71(m, 2H), 2.18 (m,3H), 2.70(s, 3H), 3.02(m, 1H), 3.15(m, 2H), 3.32(m, 3H), 3.50(m, 2H), 4.63(m, 1H), 7.05(ddd, 1H), 7.36(m, 4H), 7.56(t, 1H), 7.66(d, 1H), 8.11(s, 1H), 8.37(d, 1H)
319 (I)	(DMSO-D6) δ 1.40(m, 2H), 1.57(m, 2H), 1.79(m, 2H), 1.90(m, 2H), 2.40(m, 2H), 2.58(m, 1H), 2.79(m, 2H), 2.87(m, 2H), 4.30(d, 2H), 4.43(m, 1H), 6.97(dd,1H), 7.13(m, 2H), 7.25(d, 1H), 7.43(d, 1H), 7.49(d, 1H), 7.65(m,2H)
321 (I)	(DMSO-D6) δ 1.67 – 1.78 (m, 2H), 1.95 – 2.09 (m, 3H), 2.18 – 2.27 (m, 2H), 2.44 (d, 3H), 2.77 – 2.88 (m, 1H), 3.08 – 3.19 (m, 3H), 3.33 – 3.52

	(m, 5H), 3.59 – 3.67 (m, 1H), 4.60 – 4.68 (m, 1H), 4.84 (s, 1H), 7.05 (ddd, 1H), 7.14 – 7.27 (m, 1H), 7.37 (dd, 1H), 7.55 (t, 1H), 7.61 (q, 1H), 7.70 – 7.71 (m, 2H), 7.78 – 7.80 (m, 1H), 7.86 – 7.89 (m, 1H)
322 (I)	(DMSO-D6) δ 1.65 – 1.80 (m, 2H), 1.99 – 2.09 (m, 2H), 2.19 – 2.30 (m, 3H), 2.77 – 2.90 (m, 1H), 3.07 – 3.21 (m, 3H), 3.30 – 3.37 (m, 3H), 3.47 – 3.57 (m, 2H), 3.59 – 3.71 (m, 1H), 4.59 – 4.69 (m, 1H), 4.82 – 4.86 (m, 1H), 7.05 (ddd, 1H), 7.37 (dd, 1H), 7.49 (s, 2H), 7.55 (t, 1H), 7.64 – 7.69 (m, 2H), 7.84 – 7.86 (m, 1H), 7.92 (td, 1H)
323 (I)	(DMSO-D6) δ 1.64 – 1.78 (m, 2H), 1.99 – 2.09 (m, 2H), 2.17 – 2.29 (m, 3H), 2.70 – 2.85 (m, 1H), 3.04 – 3.19 (m, 3H), 3.28 – 3.38 (m, 3H), 3.31 (s, 3H), 3.46 – 3.55 (m, 2H), 3.66 (t, 2H), 4.12 (t, 2H), 4.56 – 4.68 (m, 1H), 4.81 – 4.86 (m, 1H), 6.94 – 6.97 (m, 2H), 7.04 (dd, 1H), 7.05 (ddd, 1H), 7.34 – 7.39 (m, 2H), 7.55 (t, 1H)
324 (I)	($CDCl_3$) δ 1.45 (s, 9H), 1.48 – 1.67 (m, 4H), 1.75 – 1.85 (m, 2H), 1.90 – 2.03 (m, 3H), 2.42 – 2.51 (m, 2H), 2.56 (m, 1H), 2.71 – 2.84 (m, 3H), 2.91 – 3.06 (m, 1H), 3.54 (q, 2H), 3.75 – 3.88 (m, 1H), 4.03 (t, 2H), 4.27 (septet, 1H), 4.68 – 4.82 (m, 1H), 4.93 – 5.01 (m, 1H), 6.75 (dd, 1H), 6.90 – 7.00 (m, 3H), 7.25 – 7.32 (m, 3H)
325 (I)	(DMSO-D6) δ 1.70 – 1.84 (m, 2H), 2.00 – 2.09 (m, 2H), 2.20 – 2.29 (m, 3H), 2.81 – 2.91 (m, 1H), 3.09 – 3.21 (m, 3H), 3.28 – 3.38 (m, 3H), 3.48 – 3.57 (m, 2H), 3.61 – 3.70 (m, 1H), 4.61 – 4.72 (m, 1H), 4.82 – 4.86 (m, 1H), 7.05 (ddd, 1H), 7.14 – 7.27 (m, 1H), 7.37 (dd,1H), 7.56 (t, 1H), 7.76 – 7.79 (m, 1H), 8.51 (s, 1H), 8.80 (d, 1H)
326 (I)	(DMSO-D6) δ 1.70 – 1.78 (m, 2H), 2.00 – 2.09 (m, 2H), 2.18 – 2.26 (m, 2H), 3.05 – 3.17 (m, 2H), 3.24 – 3.40 (m, 2H), 3.97 – 4.06 (m, 2H), 4.44 – 4.52 (m, 2H), 4.59 – 4.70 (m, 2H), 4.73 (s, 2H), 4.81 – 4.86 (m, 1H), 4.91 – 4.93 (m, 2H), 6.90 – 6.93 (m, 1H), 6.96 – 7.04 (m, 1H), 7.07 – 7.11 (m, 1H), 7.17 – 7.20 (m, 1H), 7.34 – 7.43 (m, 2H), 7.52 – 7.55 (m, 1H)
327 (I)	($CDCl_3$) δ 1.52 – 1.63 (m, 4H), 1.77 – 1.86 (m, 2H), 1.92 – 2.03 (m, 4H), 2.44 – 2.50 (m, 2H), 2.58 – 2.67 (m, 1H), 2.77 – 2.83 (m, 2H), 3.05 (bs, 1H), 3.36 (s, 3H), 4.26 – 4.31 (m, 2H), 6.74 – 6.77 (m, 1H), 6.99 – 7.01 (m, 1H), 7.30 – 7.33 (m, 1H), 7.47 (s, 1H)

328 (I)	($CDCl_3$) δ 1.43 – 1.67 (m, 4H), 1.73 – 1.91 (m, 4H), 1.95 – 2.02 (m, 2H), 2.42 – 2.50 (m, 2H), 2.52 – 2.62 (m, 1H), 2.77 – 2.85 (m, 2H), 2.92 (bs, 2H), 3.06 (s, 3H), 4.23 – 4.30 (m, 1H), 5.26 (s, 2H), 6.73 – 6.79 (m, 2H), 6.99 – 7.00 (m, 1H), 7.29 – 7.32 (m, 1H), 7.47 – 7.50 (m, 1H), 7.82 – 7.82 (m, 1H)
329 (I)	($CDCl_3$) δ 1.50 – 1.69 (m, 4H), 1.77 – 1.86 (m, 2H), 1.92 – 2.02 (m, 4H), 2.45 – 2.49 (m, 2H), 2.59 – 2.65 (m, 1H), 2.79 – 2.83 (m, 2H), 3.02 (bs, 1H), 3.39 (s, 3H), 4.26 – 4.30 (m, 2H), 5.88 (bs, 1H), 6.74 – 6.77 (m, 1H), 6.99 – 7.00 (m, 1H), 7.30 – 7.32 (m, 1H), 7.46 (bs,1H), 7.65 (s,1H)
330 (I)	(DMSO-D6) δ 1.73 – 3.63 (m, 17H), 4.57 – 4.70 (m, 1H), 7.01 – 7.88 (m, 7H)
331 (I)	(DMSO-D6) δ 1.21 (d, 6H), 1.37 – 2.03 (m, 8H), 2.33 – 3.42 (m, 7H), 4.15-4.19 (m, 1H), 4.37-4.45 (m, 1H), 5.89 (s, 2H), 6.96-8.34 (m, 4H)
332 (I)	(DMSO-D6) δ 1.41 – 1.94 (m, 8H), 2.37 – 2.78 (m, 8H), 3.32 (s, 3H), 4.38 – 4.46 (m, 1H), 6.96 – 7.78 (m, 5H)
333 (I)	($CDCl_3$) δ 1.80 – 1.96 (m, 5H), 2.38 (s, 4H), 2.41 – 3.00 (m, 12H), 3.57 – 3.60 (m, 1H), 4.26 (s, 1H), 4.73 – 4.76 (m, 1H), 6.73 – 7.32 (m, 3H)
334 (I)	(DMSO-D6) δ 1.33 – 1.93 (m, 8H), 2.33 – 3.27 (m, 7H), 4.39 – 4.45 (m, 1H), 4.49 – 4.53 (m, 1H), 6.96 – 8.98 (m, 5H)
335 (I)	($CDCl_3$) δ 1.16 – 1.30 (m, 1H), 1.33 – 1.48 (m, 1H), 1.76 – 2.75 (m, 12H), 2.96 – 3.05 (m, 1H), 3.72 (s, 2H), 3.89 – 3.93 (m, 1H), 4.21 – 4.30 (m, 1H), 4.66 – 4.71 (m, 1H), 6.72 – 7.32 (m, 7H)
336 (I)	(DMSO-D6) δ 1.37 – 2.83 (m, 17H), 4.38 – 4.47 (m, 1H), 5.76 (s, 1H), 6.96 – 7.96 (m, 6H)
337 (I)	(DMSO-D6) δ 1.33 – 1.99 (m, 8H), 2.36 – 2.60 (m, 4H), 2.73 – 2.82 (m, 2H), 2.94 (s, 3H), 2.98 – 3.09 (m, 1H), 3.55 – 3.66 (m, 1H), 4.38 – 4.46 (m, 1H), 4.56 (s, 2H), 6.96 – 7.00 (m, 1H), 7.23 – 7.27 (m, 1H), 7.41 – 7.52 (m, 5H)
338 (I)	(DMSO-D6) δ 1.35 – 1.99 (m, 8H), 2.37 – 2.46 (m, 2H), 2.55 – 2.63 (m, 2H), 2.73 – 2.85 (m, 2H), 2.92 (s, 3H), 2.97 – 3.06 (m, 1H), 3.55 – 3.65 (m, 1H), 4.41 – 4.49 (m, 1H), 4.56 (s, 2H), 6.96 – 7.01 (m, 1H), 7.25 – 7.27 (m, 1H), 7.39 – 7.52 (m, 5H)

1 (III)	δ(DMSO-D6) 1.57 – 1.36 (2H, m), 2.25 – 1.87 (5H, m), 2.45 – 2.33 (2H, m), 3.16 – 2.97 (2H, m), 3.37 – 3.17 (4H, m), 3.45 – 3.40 (1H, m), 4.12 (0H, t), 4.53 (1H, d), 4.67 – 4.58 (1H, m), 4.84 – 4.77 (1H, m), 5.45 (1H, d), 7.03 (1H, ddd), 7.19 (2H, t), 7.42 – 7.33 (3H, m), 7.55 (1H, m), 10.59 – 10.38 (1H, m)
2 (III)	δ(DMSO-D6) 1.60 – 1.36 (2H, m), 2.27 – 1.93 (5H, m), 2.61 – 2.57 (1H, m), 2.90 – 2.73 (1H, m), 3.13 – 2.94 (2H, m), 3.41 – 3.23 (3H, m), 4.17 – 3.85 (2H, m), 4.68 – 4.47 (2H, m), 4.84 – 4.77 (1H, m), 5.43 (1H, d), 7.09 – 6.99 (1H, m), 7.40 – 7.27 (6H, m), 7.55 (1H, t), 11.13 – 10.92 (1H, m)
3 (III)	δ(DMSO-D6) 1.27 – 1.07 (1H, m), 1.57 – 1.36 (1H, m), 2.24 – 1.89 (5H, m), 2.66 – 2.56 (1H, m), 2.93 – 2.79 (1H, m), 3.16 – 3.00 (2H, m), 3.51 – 3.39 (2H, m), 4.18 (1H, t), 4.67 – 4.46 (2H, m), 4.84 – 4.78 (1H, m), 5.51 – 5.43 (1H, m), 6.05 (1H, s), 7.04 (1H, dd), 7.24 – 7.17 (1H, m), 7.48 – 7.33 (3H, m), 7.55 (1H, dd), 10.41 – 10.23 (1H, m)

TABLE VII

Compound (Table)	MS	MP (°C)	^{1}H NMR	Can be prepared using:
3 (IV)	495 (M+H)	181-182	(DMSO-D6) δ 1.2-2.8 (bm, 14H), 3.1 (bm, 1H), 3.35 (s, 3H), 3.5 (bm, 1H), 4.4 (m, 1H), 4.5 (bm, 1H), 6.82 (dd, 1H), 7.1 (dd, 1H), 7.4 (t, 1H), 7.7 (m, 2H), 7.9 (s, 1H), 8.0 (dd, 1H)	Example 12
2 (IV)	495 (M+H)	111-112	(DMSO-D6) δ 1.6-2.3 (bm, 8H), 3.0-3.6 (bm, 8H), 3.3 (s, 3H), 4.5-4.8 (m, 2H), 6.9-7.1 (m, 1H), 7.2-7.4 (m, 2H), 7.8 (m, 2H), 7.94 (d,1H), 8.03 (d, 1H), 10.9 (bm, 1H)	Example 12 and final product isolated as Hydrochloride by treatment with a solution of HCl in dioxan and evaporation.
7 (IV)	459 (M+H)	149-150	(DMSO-D6) δ 1.2-3.7 (bm, 16H), 3.75 (s, 3H), 3.85 (bm, 1H), 4.6 (bm, 1H), 5.05 (bm, 1H), 6.9 (m, 4H), 7.78 (m, 2H), 7.92 (d, 1H), 8.05 (m, 1H), 11.0 and 11.8 (bm, 1H)	As for 2 (IV) above
8 (IV)	463 (M+H)	126-127	(DMSO-D6) δ 1.2-3.6 (bm, 16H), 3.9 (bm, 1H), 4.6 bm, 1H), 5.14 (bm, 1H), 7.0 (d, 2H), 7.38 (d, 2H), 7.75 (m, 2H), 7.9 (m, 1H), 8.05 (m, 1H), 11.3 and 11.95 (bm, 1H)	As for 2 (IV) above
9 (IV)	497 (M+H)	78-80	(DMSO-D6) δ 1.2-4.0 (bm, 17H), 4.6 (bm, 1H), 5.2 (bm, 1H), 7.0 (dd, 1H), 7.3 (m, 1H), 7.58 (d, 1H), 7.78 (d, 2H), 7.95 (d, 1H), 8.05 (m, 1H)11.0 and 11.65 (bm, 1H)	As for 2 (IV) above

10 (IV)	454 (M+H)	78-80	(DMSO-D6) δ 1.2-3.6 (m, 17H), 4.25 (bm, 1H), 4.98 (m, 1H), 7.03 (d, 2H), 7.72 (m, 4H), 7.9 (s, 1H), 8.0 (m, 1H)	Example 12
11 (IV)	465 (M+H)	82-83	(DMSO-D6) 1.2-3.4 (m, 16H), 3.5 (bm, 1H), 4.3 (bm, 1H), 4.85 (m, 1H), 6.7 (m, 1H), 7.0 (m, 1H), 7.3 (q, 1H), 7.7 (m, 2H), 7.9 (s, 1H), 8.0 (m, 1H)	Example 12
12 (IV)	447 (M+H)	64-65	(DMSO-D6) δ 1.2 -3.3 (m, 16H), 3.45 (bm, 1H), 4.25 (m, 1H), 4.8 (m, 1H), 6.9 (m, 2H), 7.1 (t, 2H), 7.75 (m, 2H), 7.9 (s, 1H), 8.0 (dd, 1H)	Example 12
13 (IV)	500 (M+H)	110-111	(DMSO-D6) δ 1.2-4.8 (bm, 24H), 6.95 (dd, 2H), 7.5 (m, 2H), 7.8 (m, 2H), 7.95 (s, 1H), 8.02 (d. 1H), 9.85 (d, 1H), 10.7 (bm, 1H)	As for 2 (IV) above
14 (IV)	457 (M+H)	140-142	(DMSO-D6) δ 1.2-4.8 (m, 24H), 6.86 (bm, 2H), 7.02 (m, 2H), 7.75 (bm, 2H), 7.90 (s, 1H), 8.03 (bm, 1H)	Example 12
15 (IV)	491 (M+H)	94-95	(DMSO-D6) δ 1.2-4.8 (bm, 24 H). 6.8 (bd, 1H), 7.0 (bs, 1H), 7.3 (d, 1H), 7.75 (m, 2H), 7.9 (s, 1H), 8.0 (m, 1H)	Example 12
16 (IV)	477 (M+H)	150-152	(DMSO-D6) δ 1.2- 4.6 (bm, 21H), 7.0 (bm, 2H), 7.3 (bm, 2H), 7.75 (m, 2H), 7.9 (s, 1H), 8.0 (m, 1H)	Example 12.
17 (IV)	461 (M+H)	219-220	(DMSO-D6) δ 1.2-4.8 (bm, 21 H), 6.9- 7.3 (m, 4H), 7.75 (m, 2H), 7.92 (s, 1h), 8.02 (m, 1H).	As for 2 (IV) above

18 (IV)	511 (M+H)	104-105	(DMSO-D6) δ 1.2-5.0 (bm, 21H), 7.3 (d, 1H) 7.4 (dd, 1H), 7.6 (dd, 1H), 7.75 (m, 2H), 7.95 (s, 1H), 8.0 (d, 1H), 9.5 and 9.7 (bs, 1H)	Example 12 and final product isolated as trifluoroacetate by evaporation of Reverse Phase HPLC fractions.
19 (IV)	495 (M+H)	76-77	(DMSO-D6) δ 1.2-5.0 (bm, 21H), 7.2 (m, 1H), 7.3 (m, 1H), 7.45 (m, 1H), 7.75 (m, 2H), 7.95 (s, 1H), 8.05 (m, 1H), 9.5 (bm, 1H)	As for 18 (IV) above
20 (IV)	479 (M+H)	230-232	(DMSO-D6) δ 1.2- 3.7 (bm, 19H), 4.4-4.7 (bm, 2H), 7.02 (t, 1H), 7.3 (m, 2H), 7.75 (m, 2H), 7.95 (s, 1H), 8.02 (d, 1H)	As for 2 (IV) above
21 (IV)	495 (M+H)	69-70	(DMSO-D6) 1.2-4.0 (m, 19 H), 4.4-4.8 (m, 2H), 7.3 (m, 2H), 7.5 (m, 1H), 7.75 (m, 2H), 7.98 (s, 1H), 8.0 (m, 1H), 9.5 (bm, 1H)	As for 18 (IV) above
22 (IV)	475 (M+H)	130-132	($CDCl_3$) δ.1.0-3.6 (m, 19H), 3.7(s, 3H), 4.6 (m, 2H), 6.6-6.9 (m, 3H), 7.7 (m, 2H), 8.0 (m, 2H)	As for 2 (IV) above
24 (IV)	462 (M+H)	72-73	(DMSO-D6) 1.6 (m, 2H), 1.8 (m,1H), 2.01 (m, 4H), 2.3 (m, 1H), 2.55 (m, 2H), 2.9 (m, 2H), 3.2 (m, 2H), 3.4 (m, 1H), 3.58 (m, 2H), 3.8 (s, 3H), 4.3 (bs, 2H), 4.6 and 4.8 (m, 1H), 6.7 (d, 1H), 6.8-7.0 (m, 3H), 7.2 (m, 1H), 7.5 (m, 1H), 9.5 (bs,1H)	Example 13
26 (IV)	458 (M+H)	111-112	(DMSO-D6) δ 1.4- 3.6 (m, 17H), 3.8 (2s, 6H), 4.2-4.5 (m, 3H), 6.7 (m, 2H), 6.82 (m, 2H), 6.9-7.2 (m, 2H)	Example 13
27 (IV)	440 (M+H)	73-75	(DMSO-D6) δ 1.6-1.9 (m, 3H), 2.0- 2.3 (m, 5H), 2.4-2.6 (m, 2H), 2.9 (m, 2H), 3.18 (m, 2H), 3.4 (m, 1H), 3.5 (m, 2H), 3.7 (s, 3H), 3.8 (s,	Example 13

			3H), 4.2 (bs, 2H), 4.4 and 4.6 (2m, 1H), 6.7 (d, 1H), 6.9 (m, 5H), 7.0 (d, 1H), 9.7 (bm, 1H)	
28 (IV)	462 (M+H)	81-83	(DMSO-D6) δ 1.6 (m, 2H), 1.8 (m, 1H), 2.05 (m, 4H), 2.3 (m, 1H), 2.5 (m, 1H), 2.9 (m, 2H), 3.2 (m, 2H), 3.3 (m, 2H), 3.4 (m, 1H), 3.55 (m, 2H), 3.8 (s, 3H), 4.3 (bs, 2H), 4.6 and 4.8 (m, 1H), 6.62 (d, 1H), 6.81 (d, 1H), 6.9 (s, 1H), 7.05 (m, 1H), 7.35 (m, 2H), 9.76 (bm,1H)	Example 13
29 (IV)	424 (M+H)	97-99	(DMSO-D6) δ 1.4-2.6 (m, 14H), 2.9 (m, 2H), 3.2 (m, 2H), 3.4 (m, 1H), 3.55 (m, 2H), 3.8 (s, 3H), 4.3 (bs, 2H), 4.5 and 4.7 (m, 1H), 6.65 (d, 1H), 6.9 (m, 4H), 7.1 (m, 1H), 9.5 (bs, 1H)	Example 13
30 (IV)	458 (M+H)	78-79	(DMSO-D6) δ 1.5-2.6 (m, 13H), 2.3 (s, 3H), 2.9 (m, 2H), 3.2 (m, 2H), 3.4 (m, 1H), 3.55 (m, 2H), 4.3 (bs, 2H), 4.55 and 4.75 (m, 1H), 6.67 (d, 1H), 6.85 (m, 3H), 7.0 (dd, 1H), 7.32 (t, 1H), 9.5 (bs, 1H)	Example 13
31 (IV)	444 (M+H)	100-101	(DMSO-D6) δ 1.6 (m, 2H), 1.8 (m, 1H), 2.0 (m, 4H), 2.3 (m, 1H), 2.5 (m, 2H), 2.9 (m, 2H), 3.18 (m, 2H), 3.4 (m, 1H), 3.5 (m, 2H), 3.8 (s, 3H), 4.2 (bs, 2H), 4.6 and 4.8 (m, 1H), 6.62 (d, 1H), 6.8 (m, 2H), 7.0 (m, 2H), 7.36 (m, 2H), 9.7 (bs, 1H)	Example 13
32 (IV)	428 (M+H)	74-75	(DMSO-D6) 1.6 (m, 2H), 1.8 (m, 1H), 2.0 (m, 4H), 2.3 (m, 1H), 2.5 (m, 2H), 2.9 (m, 2H), 3.2 (m, 2H), 3.4 (m, 1H), 3.5 (m, 2H), 3.8 (s, 3H), 4.2 (bs, 2H), 4.5 and 4.7 (m, 1H), 6.7 (d, 1H), 6.85 (d, 1H), 6.9 (s, 1H), 7.02 (m, 1H), 7.04 (m, 1H), 7.18 (m, 2H), 9.6 (m, 1H)	Example 13

33 (IV)	478 (M+H)	117-119	(DMSO-D6) δ 1.6-3.6 (m, 17H), 3.8 (s, 3H), 4.25 (bs, 2H), 4.6 and 4.9 (m, 1H), 6.6 (d, 1H), 6.8 (m, 2H), 7.3 (m, 1H), 7.4 (m, 1H), 7.6 (m, 1H), 9.5 (bs, 1H)	Example 13
34 (IV)	462 (M+H)	109-110	(DMSO-D6) δ 1.6-3.6 (m, 17H), 3.8 (s, 3H), 4.25 (bs, 2H), 4.55 and 4.85 (m, 1H), 6.6 (d, 1H), 6.8 (m, 2H), 7.2 (m, 1H), 7.3 (m, 1H), 7.45 (m, 1H), 9.5 (bs, 1H)	Example 13
37 (IV)	442 (M+H)	89-90	(DMSO-D6) δ 1.6-3.6 (m, 20H), 3.8 (s, 3H), 4.25 (bs, 2H), 4.45 and 4.75 (m, 1H), 6.6 (d, 1H), 6.8 (m, 2H), 7.0 (m, 3H), 9.6 (bs, 1H)	Example 13
38 (IV)	471 (M+H)	143-145	(DMSO-D6) δ 1.6-3.6 (m, 19H), 4.2-4.8 (m, 2H), 7.0 (m, 1H), 7.2 (d, 1H), 7.22 (s, 1H), 7.8 (d, 1H), 8.5 (d, 1H), 8.8 (s, 1H)	As for 18 (IV) above
39 (IV)	475 (M+H)	141-142	(DMSO-D6) δ 1.6-3.6 (m, 16H), 4.2-4.8 (m, 2H), 6.9 (m, 1H), 7.2 (m, 1H), 7.5 (m, 1H), 7.8 (d, 1H), 8.5 (d, 1H), 8.8 (d, 1H)	As for 18 (IV) above
41 (IV)	471 (M+H)	160-162	(DMSO-D6) δ 1.6-3.6 (m, 16H), 3.8 (s, 3H), 4.2-4.8 (m, 2H), 6.7 (m, 1H), 6.9-7.2 (m, 2H), 7.8 (d, 1H), 8.5 (d, 1H), 8.8 (d, 1H)	As for 18 (IV) above
42 (IV)	453 (M+H)	116-118	(DMSO-D6) δ 1.6-3.6 (m, 16H), 3.7 (s, 3H), 4.2-4.8 (m, 2H), 6.8-7.1 (m, 3H), 7.82 (d, 1H), 8.52 (d, 1H), 8.8 (d, 1H), 9.6 (bs, 1H)	As for 18 (IV) above
43 (IV)	475 (M+H)	109-110	(DMSO-D6) δ 1.6-3.6 (m, 16H), 4.2-4.8 (m, 2H), 7.07 (m, 1H), 7.35 (m, 2H), 7.82 (d, 1H), 8.52 (d, 1H), 8.8 (d, 1H), 9.6 (bs, 1H)	As for 18 (IV) above
44 (IV)	437 (M+H)	136-137	(DMSO-D6) δ 1.6-3.2 (m, 15H), 3.3 (s, 3H), 3.6 (m, 1H), 4.22 (m, 1H), 4.5 (m, 1H), 6.8 (d, 2H), 7.10 (d, 2H), 7.82 (d, 1H), 8.52 (d, 1H),	Example 12

			8.8 (d, 1H)	
89 (IV)	471 (M+H)	100-102	(DMSO-D6) δ 1.0-4.2 (m, 21H), 6.0 (m, 1H), 6.18 (m, 1H), 6.42 (m, 1H), 7.02 (d, 1H), 7.6 (d, 1H), 7.85(d, 1H)	As for 18 (IV) above
47 (IV)	441 (M+H)	133-136	(DMSO-D6) δ 1.6-4.8 (m, 18H), 6.9-7.2 (m, 4H), 7.82 (d, 1H), 8.52 (d, 1H), 8.8 (d, 1H)	As for 18 (IV) above
48 (IV)	491 (M+H)	105-106	(DMSO-D6) δ 1.6-4.8 (m, 18H), 6.3 (d, 1H), 6.4 (d, 1H), 6.58 (s, 1H), 6.9 (d, 1H), 7.52 (d, 1H), 7.8 (d, 1H)	As for 18 (IV) above
49 (IV)	475 (M+H)	123-125	(DMSO-D6) δ 1.6-4.8 (m, 18H), 7.2 (m, 1H), 7.3 (m, 1H), 7.45 (m, 1H), 7.82(d, 1H), 8.52 (d, 1H), 8.8 (d, 1H)	As for 18 (IV) above
50 (IV)	459 (M+H)	93-94	(DMSO-D6) δ 1.6-4.8 (m, 18H), 7.05(m, 1H), 7.3 (m, 2H), 7.82(d, 1H), 8.52 (d, 1H), 8.8 (d, 1H), 9.7 (bm, 1H)	As for 18 (IV) above
271 (IV)	507 (M+H)	102-103	(DMSO-D6) δ 1.6-3.8 (m, 16H), 3.3 (s, 3H), 3.8 (d, 3H), 4.4-4.7 (m, 2H), 6.95 (m, 1H), 7.1 (m, 2H), 7.78 (m, 2H), 7.95 (s, 1H), 8.03 (d, 1H)	Example 12
272 (IV)	505 (M+H)	97-98	(DMSO-D6) δ 1.6-4.8 (m, 27H), 7.1 (s, 2H), 7.6 (m, 2H), 7.95 (s, 1H), 8.03 (d, 1H)	As for 18 (IV) above
273 (IV)	511 (M+H)	110-112	(DMSO-D6) δ 1.4-3.8 (m, 16H), 3.3 (s, 3H), 4.4-5.0 (m, 2H), 7.22 (m, 2H), 7.3 (m, 1H), 7.75 (m, 2H), 7.95 (s, 1H), 8.02 (d, 1H)	As for 18 (IV) above
274 (IV)	511 (M+H)	114-115	(DMSO-D6) δ 1.4-3.8 (m, 16H), 3.3 (s, 3H), 4.4-5.0 (m, 2H), 7.02 (m, 1H), 7.4 (m, 2H), 7.75 (m, 2H), 7.95 (s, 1H), 8.02 (d, 1H)	Example 12

275 (IV)	491 (M+H)	88-89	(DMSO-D6) δ 1.4-3.8 (m, 16H), 2.25 (s, 3H), 3.3 (s, 3H), 4.2-4.8 (m, 2H), 7.02 (m, 2H), 7.22 (m, 1H), 7.75 (m, 2H), 7.95 (s, 1H), 8.02 (d, 1H)	Example 12
276 (IV)	491 (M+H)	182-183	(DMSO-D6) δ 1.4-3.8 (m, 16H), 2.25 (s, 3H), 3.3 (s, 3H), 4.4-4.6 (m, 2H), 6.74 (d, 1H), 7.02 (s, 1H), 7.22 (d, 1H), 7.75 (m, 2H), 7.90 (s, 1H), 8.0 (d, 1H)	Example 12
277 (IV)	499 (M+H)	162-164	(DMSO-D6) δ 1.6-3.8 (m, 19H), 2.25 (s, 3H), 3.3 (s, 3H),4.5-5.0 (m, 2H), 7.14 (t, 1H), 7.8 (m, 4H), 7.95 (m,1H), 8.02 (d, 1H), 10.9 (bm, 1H)	As for 2 (IV) above
278 (IV)	528 (M+H)	120-122	(DMSO-D6) δ 1.5-5.0 (m, 29H), 6.9-7.2 (m, 4H), 7.75 (m, 2H), 7.95 (s, 1H), 8.02 (d, 1H), 10.2 (bs, 1H), 11.0-11.3 (bm, 1H)	As for 2 (IV) above
279 (IV)	505 (M+H)	97-99	(DMSO-D6) δ 1.18 (t, 3H), 1.6-3.7 (m, 17H), 2.62 (q, 2H), 3.3 (s, 3H), 4.4-4.8 (m, 1H), 6.8-7.1 (m, 2H), 7.3 (m, 1H), 7.75 (m, 2H), 7.95 (s, 1H), 8.02 (m, 1H), 9.4 (bs, 1H)	Example 12
280 (IV)	494 (M+H)	138-140	(DMSO-D6) δ 1.8 (m, 2H), 2.1-4.4 (m, 14H), 3.3 (s, 3H), 4.62 (bm, 1H), 4.9 and 5.1 (m, 1H), 7.65 (m, 1H), 7.8 (m, 2H), 7.85 (m, 2H), 7.95 (d, 1H), 8.01 (d, 1H), 8.3 (t, 1H), 9.0 (t, 1H), 9.15 (t, 1H), 10.35 (bs, 1H), 11.5 (bs, 1H)	As for 2 (IV) above
281 (IV)	499 (M+H)	98-99	(DMSO-D6) δ 1.2 (s, 9H), 1.3-3.6 (m, 20H), 4.5 (m, 1H), 6.8 (t, 1H), 6.9 (d, 1H), 7.1 (t, 1H), 7.2 (d, 1H), 7.7 (m, 2H), 7.9 (s, 1H), 8.0 (d,	Example 12

			1H)	
282 (IV)	483 (M+H)	79-80	(DMSO-D6) δ 1.2-3.6 (m, 22H), 3.3 (s, 3H), 4.22 and 4.5 (m, 2H), 6.67 (d, 1H), 6.8 (s, 1H), 7.08 (d, 1H), 7.75 (m, 2H), 7.9 (s, 1H), 8.0 (d, 1H)	Example 12
283 (IV)	559 (M+H)	113-115	(DMSO-D6) δ 1-1.48 (m, 29H), 3.3 (s, 3H), 7.0 (m, 1H), 7.18 (m, 2H), 7.75 (m, 2H), 7.9 (s, 1H), 8.0 (m, 1H)	Example 12
284 (IV)	520 (M+H)	111-112	(DMSO-D6) δ 1.6-4.0 (m, 19H), 4.6 and 4.9 (m, 2H), 7.2 (m, 1H), 7.4-7.8 (m, 6H), 7.95 (s, 1H), 8.02 (d, 1H), 9.5 (bm, 1H)	As for 18 (IV) above
285 (IV)	544 (M+H)	111-112	(DMSO-D6) δ 1.6-3.2 (m, 15H), 3.3 (s, 3H), 3.5 (m, 1H), 4.5 and 4.6 (m, 2H), 6.9 (d, 1H), 7.35 (d, 1H), 7.5 (dd, 1H), 7.75 (m, 2H), 7.81 (d, 1H), 7.9 (s, 1H), 8.0 (dd, 1H), 8.68 (d, 1H)	Example 12
286 (IV)	491 (M+H)	115-117	(DMSO-D6) δ 1.6-3.2 (m, 16H), 3.3 (s, 3H), 3.35-3.6 (m, 3H), 4.4 - 4.9 (m, 2H), 6.9 (m, 1H), 7.0-7.2 (m, 2H), 7.75 (m, 2H), 7.92 (s, 1H), 8.02 (m, 1H)	Example 12
287 (IV)	443 (M+H)	142-144	(DMSO-D6) δ 1.6-3.4 (m, 14H), 3.3 (s, 3H), 3.4-3.7 (m, 2H), 4.6 - 4.8 (m, 2H), 7.0 (m, 3H), 7.3 (m, 2H), 7.75 (m, 2H), 7.92 (s, 1H), 8.04 (dd, 1H)	Example 12
288 (IV)	525 (M+H)	84-86	(DMSO-D6) δ 1.6-3.4 (m, 22H), 4.2 - 4.7 (m, 2H), 7.38 (d, 1H), 7.5 (d, 1H), 7.75 (m, 2H), 7.95 (s, 1H), 8.02 (m, 1H)	As for 18 (IV) above

289 (IV)	491 (M+H)	149-151	(DMSO-D6) δ 1.3-2.0 (m, 8H),2.22 (s, 3H), 2.3-2.6 (m, 4H), 2.8 (m, 2H), 3.1 (m, 1H), 3.3 (s,3H), 3.5 (m, 1H), 4.3-4.6 (m, 2H), 6.84 (dd, 1H), 7.0 (d, 1H),7.2 (m, 1H), 7.75 (m, 2H), 7.9 (s, 1H), 8.0 (dd, 1H)	Example 12
290 (IV)	502 (M+H)	93-95	(DMSO-D6) δ 1.6-4.0 (m, 16H), 3.3 (s, 3H), 4.4-5.1 (m, 2H), 7.4 (t, 1H), 7.8 (m, 3H), 7.9-8.1 (m, 3H), 9.5-10.0 (bm, 1H)	As for 18 (IV) above
293 (IV)	445 (M+H)	66-68	(DMSO-D6) δ 1.6-3.0 (m, 7H), 2.8 (m, 1H), 3.2 (m, 3H), 3.3 (s, 3H), 3.4-3.7 (m, 4H), 4.62 (m, 1H), 5.1- 5.4 (m, 2H), 7.2 (m, 1H), 7.8 (m, 2H), 7.95 (m, 1H), 8.02 (d, 1H), 8.6 (m, 2H), 9.5 (bs, 1H)	Example 15
339 (I)	(M+H) 458	foam	(DMSO-D6) δ 1.42 - 1.70 (m, 5H), 1.84 - 1.94 (m, 3H), 2.35 – 2.42 (m, 2H), 2.54 - 2.62 (m, 1H), 2.73 - 2.87 (m, 3H), 3.02 – 3.10 (m, 1H), 3.30 - 3.36 (m, 1H), 4.39 - 4.44 (m, 1H), 4.53 – 4.57 (m, 1H), 6.95 - 6.99 (m, 1H), 7.24 - 7.25 (m, 1H), 7.47 – 7.50 (m, 1H), 7.56 - 7.67 (m, 2H), 7.77 - 7.82 (m, 1H), 7.94 – 7.96 (m, 1H)	Example 2 step c
340 (I)	(M+H) 484	156-157	(DMSO-D6) δ 1.40 - 1.99 (m, 8H), 2.35 - 2.46 (m, 2H), 2.54 – 2.62 (m, 1H), 2.73 - 2.85 (m, 3H), 3.02 - 3.13 (m, 1H), 3.60 – 3.72 (m, 1H), 4.39 - 4.47 (m, 1H), 4.51 - 4.64 (m, 1H), 6.96 – 7.00 (m, 1H), 7.25 - 7.26 (m, 1H), 7.50 (d, 1H), 7.59 - 7.63 (m, 1H), 7.74 - 7.78 (m, 1H), 8.06 - 8.09 (m, 2H), 8.45 - 8.48 (m, 1H), 8.96 - 8.98 (m, 1H)	Example 2 step c

341 (I)	(M+H) 485	127-129	(DMSO-D6) δ 1.44 - 1.99 (m, 8H), 2.40 - 2.48 (m, 2H), 2.58 – 2.67 (m, 1H), 2.75 - 2.90 (m, 3H), 3.04 - 3.16 (m, 1H), 3.56 – 3.69 (m, 1H), 4.40 - 4.49 (m, 1H), 4.53 - 4.63 (m, 1H), 6.96 – 7.00 (m, 1H), 7.26 - 7.27 (m, 1H), 7.48 - 7.51 (m, 1H), 7.85 – 7.88 (m, 1H), 8.09 - 8.11 (m, 1H), 8.16 - 8.19 (m, 1H), 9.01 (s, 2H)	Example 2 step c using Quinoxaline-6-carboxylic acid (obtained from hydrolysis of the commercially available Quinoxaline-6-carboxylic acid methyl ester)
342 (I)	(M+H) 532	foam	(DMSO-D6) δ 1.36 - 1.44 (2H, m), 1.55 - 1.61 (2H, m), 1.76 – 1.82 (2H, m), 1.89 - 1.96 (2H, m), 2.34 - 2.41 (3H, m), 2.72 – 2.80 (2H, m), 2.95 (2H, t), 3.21 (3H, s), 4.15 - 4.22 (2H, m), 4.38 - 4.46 (1H, m), 5.87 (2H, s), 6.96 - 6.99 (2H, m), 7.24 – 7.26 (2H, m), 7.49 (1H, d), 8.34 (1H, s)	Example 2 step c using 3-Amino-4-methanesulfonyl-thiophene-2-carboxylic acid (obtained from hydrolysis of the commercially available 3-Amino-4-methanesulfonyl-thiophene-2-carboxylic acid methyl ester)
63 (IV)	491 (M+H)	127-129	(DMSO-D6) δ 1.42 - 1.96 (8H, m), 2.26 (3H, s), 2.32 - 2.41 (2H, m), 2.53 - 2.59 (2H, m), 2.67 - 3.11 (4H, m), 3.24 (3H, s), 4.28 - 4.35 (2H, m), 6.77 - 6.81 (1H, m), 6.95 (1H, d), 7.26 (1H, dd), 7.50 (1H, ddd), 7.70 (1H, d), 7.76 - 7.82 (1H, m), 7.98 (1H, ddd)	Example 2 step c
79 (IV)	497 (M+H)	168-169	(DMSO-D6) δ 1.41 - 1.49 (2H, m), 1.53 - 1.60 (2H, m), 1.80 (2H, d), 1.92 (2H, dz), 2.27 (3H, s), 2.38 (2H, t), 2.54 - 2.62 (2H, m), 2.77 (2H, t), 2.93 - 3.12 (2H, m), 3.40 (3H, s), 4.33 (2H, dt), 6.80 (1H, dd), 6.95 (1H, d), 7.26 (1H, d), 7.49 (1H, d), 7.77 (1H, d)	Example 2 step c

423 (I)	(M+H) 499	181-183	(DMSO-D^6) δ 1.44 - 1.63 (6H, m), 1.91 - 1.98 (3H, m), 2.36 – 2.39 (2H, m), 2.53 - 2.62 (4H, m), 2.76 - 2.90 (2H, m), 3.03 – 3.11 (1H, m), 3.34 - 3.42 (1H, m), 4.40 - 4.45 (1H, m), 4.56 – 4.64 (1H, m), 6.96 - 6.99 (1H, m), 7.24 (1H, s), 7.48 - 7.51 (1H, m), 7.61 - 7.65 (1H, m), 8.39 - 8.47 (2H, m), 9.06 - 9.08 (1H, m)	Example 2 step c
578 (I)	(M+H) 473	145-147	(DMSO-D^6) δ 1.33 - 1.45 (2H, m), 1.53 - 1.64 (2H, m), 1.76 – 1.94 (4H, m), 2.36 - 2.44 (2H, m), 2.55 - 2.64 (1H, m), 2.70 – 2.80 (3H, m), 3.03 - 3.15 (1H, m), 4.35 - 4.44 (1H, m), 4.51 – 4.61 (1H, m), 5.08 - 5.20 (1H, m), 6.93 - 7.00 (2H, m), 7.25 – 7.34 (2H, m), 7.45 - 7.50 (1H, m), 7.57 - 7.63 (1H, m), 8.33 (1H, s), 8.50 - 8.62 (1H, m)	Example 2 step c
580 (I)	(M+H) 500	>200	(DMSO-D^6) δ 1.43 - 1.65 (4H, m), 1.85 - 1.96 (3H, m), 2.32 – 2.41 (2H, m), 2.54 - 2.62 (2H, m), 2.73 - 3.14 (4H, m), 3.40 – 3.47 (1H, m), 4.37 - 4.45 (1H, m), 4.53 - 4.62 (1H, m), 6.45 (1H, d), 6.93 - 7.00 (1H, m), 7.17 - 7.26 (2H, m), 7.33 - 7.59 (4H, m), 11.99 (1H, s)	Example 2 step c
419 (I)	(M+H) 464	>200	(DMSO-D^6) δ 1.25 - 1.68 (5H, m), 1.72 - 1.81 (2H, m), 1.88 – 1.95 (2H, m), 2.22 (3H, s), 2.31 - 2.40 (2H, m), 2.60 - 2.78 (3H, m), 2.92 - 3.00 (1H, m), 3.44 - 3.52 (1H, m), 4.36 - 4.49 (2H, m), 5.92 - 6.11 (1H, m), 6.91 - 7.06 (1H, m), 7.25 (1H, s), 7.30 – 7.41 (1H, m), 7.44 - 7.54 (1H, m), 11.86 (1H, s)	Example 2 step c

550 (I)	(M+H) 484	80-85	(DMSO-D^6) δ 1.40 - 1.65 (5H, m), 1.83 - 1.96 (3H, m), 2.31 – 2.43 (2H, m), 2.50 - 2.56 (1H, m), 2.69 - 2.92 (4H, m), 3.08 – 3.17 (1H, m), 4.36 - 4.42 (1H, m), 4.65 - 4.75 (1H, m), 6.94 – 7.00 (1H, m), 7.19 - 7.25 (1H, m), 7.45 - 7.50 (1H, m), 7.58 – 7.71 (3H, m), 8.00 - 8.05 (1H, m), 8.39 - 8.46 (1H, m), 8.91 – 8.96 (1H, m)	Example 2 step c
426 (I)	(M+H) 464	158-159	(DMSO-D6) δ 1.36 - 1.45 (2H, m), 1.53 - 1.61 (2H, m), 1.72 – 1.79 (2H, m), 1.88 - 1.96 (2H, m), 2.35 - 2.43 (2H, m), 2.52 – 2.57 (1H, m), 2.72 - 2.79 (2H, m), 2.85 - 2.94 (2H, m), 3.32 – 3.38 (1H, m), 3.49 (3H, s), 3.99 - 4.12 (1H, m), 4.34 - 4.51 (1H, m), 6.36 (1H, d), 6.90 - 7.06 (1H, m), 7.21 - 7.29 (1H, m), 7.42 - 7.54 (2H, m), 7.91 - 8.03 (1H, m)	Example 2 step c
416 (I)	(M+H) 448	133-135	(DMSO-D6) δ 1.38 - 1.45 (2H, m), 1.53 - 1.60 (2H, m), 1.66 – 1.84 (2H, m), 1.88 - 1.95 (2H, m), 2.34 - 2.41 (2H, m), 2.51 – 2.58 (1H, m), 2.73 - 2.78 (3H, m), 3.01 - 3.10 (1H, m), 3.29 – 3.36 (3H, m), 3.53 - 3.63 (1H, m), 4.38 - 4.53 (2H, m), 6.94 – 7.01 (1H, m), 7.21 - 7.28 (1H, m), 7.29 - 7.35 (1H, m), 7.47 – 7.52 (1H, m), 7.68 - 7.75 (1H, m), 8.42 - 8.50 (1H, m)	Example 2 step c
575 (I)	(M+H) 645	140-142		Example 2 step c

534 (I)	(M+H) 543	189-190		Example 2 step c
294 (IV)	(M+H) 529	foam	($CDCl_3$) δ 1.32 - 1.45 (1H, m), 1.56 - 1.71 (2H, m), 1.79 - 2.01 (5H, m), 2.46 - 2.61 (3H, m), 2.79 - 2.87 (3H, m), 2.92 - 3.16 (4H, m), 3.36 - 3.42 (1H, m), 4.28 - 4.33 (1H, m), 4.79 (1H, t), 6.90 (2H, dd), 7.12 (1H, dt), 7.49 (1H, dd), 7.89 (1H, ddd), 8.01 (1H, dd)	Example 2 step c
67 (IV)	(M+H) 495	132-133	($CDCl_3$) δ 1.38 - 1.65 (2H, m), 1.73 - 2.04 (6H, m), 2.40 - 2.67 (3H, m), 2.72 - 2.89 (3H, m), 2.99 - 3.08 (1H, m), 3.23 - 3.28 (3H, m), 3.33 - 3.53 (1H, m), 4.21 - 4.33 (1H, m), 4.61 - 4.86 (1H, m), 6.87 - 6.92 (2H, m), 7.10 - 7.14 (1H, m), 7.31 - 7.37 (1H, m), 7.55 - 7.70 (2H, m), 8.07 (1H, td)	Example 2 step c
83 (IV)	(M+H) 501	foam	($CDCl_3$) δ 1.50 - 1.63 (2H, m), 1.85 - 2.00 (6H, m), 2.44 - 2.51 (2H, m), 2.56 - 2.66 (1H, m), 2.80 - 2.88 (2H, m), 3.01 (2H, s), 3.20 (3H, s), 4.27 - 4.51 (3H, m), 6.91 (2H, dd), 7.13 (1H, dt), 7.23 (1H, d), 7.63 (1H, d)	Example 2 step c
295 (IV)	(M+H) 491		($CDCl_3$) δ 1.75 - 2.03 (10H, m), 2.18 - 2.19 (3H, m), 2.44 - 2.54 (2H, m), 2.77 - 2.89 (3H, m), 3.00 - 3.09 (1H, m), 3.23 - 3.28 (3H, m), 3.36 - 3.52 (1H, m), 4.63 - 4.85 (1H, m), 6.70 - 6.75 (1H, m), 7.05 - 7.11 (2H, m), 7.31 - 7.37 (1H, m), 7.56 - 7.68 (2H, m), 8.05 - 8.10 (1H, m)	Example 2 step c

568 (I)	(M+H) 558		(DMSO-D6) δ 1.21 - 1.95 (8H, m), 2.35 - 2.42 (2H, m), 2.57 – 2.66 (1H, m), 2.72 - 2.77 (2H, m), 3.08 - 3.17 (1H, m), 4.08 – 4.13 (1H, m), 4.29 (2H, d), 4.40 - 4.46 (3H, m), 6.96 - 7.00 (1H, m), 7.25 - 7.26 (1H, m), 7.48 - 7.51 (1H, m), 7.58 - 7.62 (1H, m), 8.01 - 8.07 (2H, m), 8.40 - 8.43 (1H, m), 8.75 - 8.78 (2H, m)	Example 2 step c
296 (IV)	(M+H) 525		($CDCl_3$) δ 1.58 - 1.68 (4H, m), 1.85 (2H, s), 2.00 (2H, s), 2.19 (3H, s), 2.51 - 2.59 (3H, m), 2.80 - 2.92 (3H, m), 2.98 - 3.16 (4H, m), 3.37 - 3.43 (1H, m), 4.33 (1H, s), 4.76 - 4.85 (1H, m), 6.72 - 6.74 (1H, m), 7.06 - 7.12 (2H, m), 7.45 - 7.53 (1H, m), 7.88 - 7.91 (1H, m), 8.00 - 8.02 (1H, m)	Example 2 step c
471 (I)	472 (M+H)		δ 1.40(m, 2H), 1.57(m, 2H), 1.79(m, 2H), 1.90(m, 2H), 2.40(m, 2H), 2.58(m, 1H), 2.79(m, 2H), 2.87(m, 2H), 4.30(d, 2H), 4.43(m, 1H), 6.97(dd,1H), 7.13(m, 2H), 7.25(d, 1H), 7.43(d, 1H), 7.49(d, 1H), 7.65(m,2H)	Example 2 step c
475(I)	526 (M+H)		(DMSO-D6) δ 1.67 - 1.78 (m, 2H), 1.95 - 2.09 (m, 3H), 2.18 – 2.27 (m, 2H), 2.44 (d 3H), 2.77 - 2.88 (m, 1H), 3.08 - 3.19 (m, 3H), 3.33 - 3.52 (m, 5H), 3.59 - 3.67 (m, 1H), 4.60 - 4.68 (m, 1H), 4.84 (s, 1H), 7.05 (ddd, 1H), 7.14 - 7.27 (m, 1H), 7.37 (dd, 1H), 7.55 (t, 1H), 7.61 (q, 1H), 7.70 - 7.71 (m, 2H), 7.78 - 7.80 (m, 1H), 7.86 - 7.89 (m, 1H),	Example 2 step c

569(I)	512 (M+H)		(DMSO-D6) δ 1.65 - 1.80 (m, 2H), 1.99 - 2.09 (m, 2H), 2.19 – 2.30 (m, 3H), 2.77 - 2.90 (m, 1H), 3.07 - 3.21 (m, 3H), 3.30 – 3.37 (m, 3H), 3.47 - 3.57 (m, 2H), 3.59 - 3.71 (m, 1H), 4.59 – 4.69 (m, 1H), 4.82 - 4.86 (m, 1H), 7.05 (ddd, 1H), 7.37 (dd, 1H), 7.49 (s, 2H), 7.55 (t, 1H), 7.64 - 7.69 (m, 2H), 7.84 - 7.86 (m, 1H), 7.92 (td, 1H)	Example 2 step c
477(I)	507 (M+H)		(DMSO-D6) δ 1.64 - 1.78 (m, 2H), 1.99 - 2.09 (m, 2H), 2.17 – 2.29 (m, 3H), 2.70 - 2.85 (m, 1H), 3.04 - 3.19 (m, 3H), 3.28 – 3.38 (m, 3H), 3.31 (s, 3H), 3.46 - 3.55 (m, 2H), 3.66 (t, 2H), 4.12 (t, 2H), 4.56 - 4.68 (m, 1H), 4.81 - 4.86 (m, 1H), 6.94 – 6.97 (m, 2H), 7.04 (dd, 1H), 7.05 (ddd, 1H), 7.34 - 7.39 (m, 2H), 7.55 (t, 1H),	Example 2 step c
584(I)	592 (M+H)		($CDCl_3$) δ 1.45 (s, 9H), 1.48 - 1.67 (m, 4H), 1.75 - 1.85 (m, 2H), 1.90 - 2.03 (m, 3H), 2.42 - 2.51 (m, 2H), 2.56 (m, 1H), 2.71 - 2.84 (m, 3H), 2.91 - 3.06 (m, 1H), 3.54 (q, 2H), 3.75 – 3.88 (m, 1H), 4.03 (t, 2H), 4.27 (septet, 1H), 4.68 - 4.82 (m, 1H), 4.93 - 5.01 (m, 1H), 6.75 (dd, 1H), 6.90 - 7.00 (m, 3H), 7.25 - 7.32 (m, 3H)	Example 2 step c
325 (I)	491 (M+H)		(DMSO-D6) δ 1.69 - 1.83 (2H, m), 1.98 - 2.11 (3H, m), 2.17 – 2.28 (3H, m), 2.81 - 2.92 (1H, m), 3.08 - 3.21 (3H, m), 3.47 – 3.59 (2H, m), 3.61 - 3.71 (1H, m), 4.61 - 4.73 (2H, m), 4.82 – 4.86 (1H, m), 7.05 (1H, ddd), 7.37 (1H, dd), 7.56 (1H, t), 7.77 (1H, ddd), 8.51 (1H, s), 8.80 (1H, d)	Example 2 step c using acid prepared according to Journal of Heterocyclic chemistry, 1972, p1149

585 (I)	507 (M+H)		(DMSO-D6) δ 1.70 - 1.78 (m, 2H), 2.00 - 2.09 (m, 2H), 2.18 – 2.26 (m, 2H), 3.05 - 3.17 (m, 2H), 3.24 - 3.40 (m, 2H), 3.97 – 4.06 (m, 2H), 4.44 - 4.52 (m, 2H), 4.59 - 4.70 (m, 2H), 4.73 (s, 2H), 4.81 - 4.86 (m, 1H), 4.91 - 4.93 (m, 2H), 6.90 - 6.93 (m, 1H), 6.96 - 7.04 (m, 1H), 7.07 - 7.11 (m, 1H), 7.17 - 7.20 (m, 1H), 7.34 - 7.43 (m, 2H), 7.52 - 7.55 (m, 1H),	Example 2 step c, using 3-tert-butoxycarbonylmethoxy-benzoic acid, followed by the addition of (1M) HCl in ether to form final compound as hydrochloride salt. (HCl also cleaved tert-butyl ester to leave acid.)
586 (I)	492 (M+H)		(DMSO-D6) δ 1.56-1.87 (3H, m), 1.94-2.17 (5H, m), 3.06-3.27 (7H, m), 3.50-3.78 (3H, m), 4.19 (2H, t), 4.57-4.69 (1H, m), 4.80-4.85 (1H, m), 6.98-7.10 (4H, m), 7.34-7.44 (2H, m), 7.57 (1H, dd)	Prepared by deprotection of 584(I) using trifluoroacetic acid in dichloromethane
588 (I)	551 (M+H)	145	($CDCl_3$) δ 0.09 (2H, dd), 0.44 (2H, dd), 0.83 – 0.89 (1H, m), 1.67 - 1.78 (2H, m), 1.96 - 2.09 (3H, m), 2.18 - 2.28 (4H, m), 2.78 - 2.89 (1H, m), 3.08 - 3.20 (4H, m), 3.34 (2H, s), 3.47 – 3.65 (3H, m), 4.59 - 4.68 (1H, m), 4.84 (1H, s), 7.05 (1H, ddd), 7.36 (1H, dd), 7.55 (1H, t), 7.73 - 7.81 (2H, m), 7.90 (1H, t), 8.00 (1H, d)	Example 2 step c
71 (IV)	497 (M+H)		($CDCl_3$) δ 1.56 (2H, qd), 1.79 - 1.99 (8H, m), 2.19 (3H, s), 2.45 - 2.52 (2H, m), 2.60 (1H, tt), 2.76 - 2.83 (2H, m), 2.91 - 3.11 (2H, m), 3.21 (3H, s), 4.28 - 4.35 (1H, m), 6.74 (1H, d), 7.05 – 7.12 (2H, m), 7.24 (1H, d), 7.63 (1H, d)	Example 2 step c

245 (IV)	486 (M+H)	120-126	($CDCl_3$) δ 1.45 - 1.61 (2H, m), 1.80 - 2.03 (6H, m), 2.19 (3H, s), 2.45 - 2.53 (2H, m), 2.54 - 2.62 (1H, m), 2.79 - 3.09 (4H, m), 3.80 - 3.99 (1H, m), 4.28 - 4.34 (1H, m), 4.62 - 4.81 (1H, m), 6.73 (1H, d), 7.05 - 7.12 (3H, m), 7.30 (1H, dd), 7.47 (1H, d)	Example 2 step c using 2-Oxo-2,3-dihydro-benzothiazole-6-carboxylic acid prepared according to Chem. Pharm. Bull. 1988, 36, p2253
297 (IV)	526 (M+H)	115-117	($CDCl_3$) δ 1.42 - 1.64 (2H, m), 1.78 - 1.87 (3H, m), 1.93 - 2.01 (3H, m), 2.19 (3H, s), 2.44 - 2.51 (2H, m), 2.57 (1H, tt), 2.75 – 2.88 (3H, m), 3.01 - 3.14 (1H, m), 3.64 - 3.73 (1H, m), 4.27 – 4.33 (1H, m), 4.65 - 4.74 (1H, m), 6.73 (1H, d), 7.07 (1H, dd), 7.11 (1H, d), 7.52 (1H, dd), 7.58 (1H, d), 8.11 (1H, d)	Example 2 step c
298 (IV)	480 (M+H)	120-126	($CDCl_3$) δ 1.31 - 1.66 (2H, m), 1.70 - 2.05 (6H, m), 2.19 (3H, s), 2.38 - 2.60 (3H, m), 2.73 - 2.83 (2H, m), 2.85 - 3.11 (2H, m), 3.71 - 3.86 (1H, m), 4.26 - 4.35 (1H, m), 4.76 - 4.92 (1H, m), 6.73 (1H, d), 7.07 (1H, dd), 7.11 (1H, s), 7.19 - 7.34 (1H, m), 7.57 (1H, t), 7.59 - 7.68 (1H, m), 7.73 (1H, t), 8.46 (1H, d)	Example 2 step c
214 (IV)	514 (M+H)	96	($CDCl_3$) δ 1.42 - 1.62 (2H, m), 1.74 - 2.02 (6H, m), 2.19 (3H, s), 2.44 - 2.61 (3H, m), 2.75 - 2.85 (3H, m), 2.95 - 3.11 (1H, m), 3.42 (2H, s), 3.45 (3H, s), 3.78 - 3.93 (1H, m), 4.26 - 4.36 (1H, m), 4.64 - 4.81 (1H, m), 6.74 (1H, d), 7.02 - 7.15 (3H, m), 7.27 (1H, s), 7.38 (1H, d)	Example 2 step c
589 (I)	540 (M+H)		($CDCl_3$) δ 1.52 - 1.62 (2H, m), 1.68 (1H, d), 1.84 (1H, d), 1.92 (2H, d), 2.35 - 2.42 (2H, m), 2.52 - 2.55 (1H, m), 2.63 (6H, s), 2.72 - 2.83 (3H, m), 2.99 - 3.13 (2H, m), 3.46 - 3.56 (2H, m), 4.38 - 4.45 (1H, m), 4.49 (1H, d), 6.98 (1H, dd), 7.25 (1H, d), 7.49 (1H, d), 7.73 - 7.75 (2H, m), 7.81 - 7.83 (1H, m), 8.31 (1H, s)	
590(I)	556 (M+H)		(DMSO-D6) δ 1.43 - 1.62 (4H, m), 1.66 (1H, d), 1.85 (1H, d), 1.89 - 1.97 (2H, m), 2.35 - 2.44 (3H, m), 2.73 - 2.87 (3H, m), 3.11 (1H, t), 3.42 (3H, s), 3.52 (1H, d), 4.39 - 4.46 (1H, m), 4.50 (1H, d), 6.98 (1H, dd), 7.25 (1H, d), 7.49 (1H, d), 8.36 (1H, t), 8.54 (1H, t), 8.67 (1H, t)	Example 2 step c
591 (I)	526 (M+H)		(DMSO-D6) δ 1.29 - 1.39 (2H, m), 1.90 (2H, d), 2.11 - 2.18 (1H, m), 2.39 (2H, t), 3.13 (2H, t), 3.44 - 3.52 (2H, m), 3.65 – 3.73 (2H, m), 3.82 - 3.91 (4H, m), 3.94 - 4.01 (2H, m), 4.47 – 4.57 (1H, m), 6.15 (1H, d), 6.88 - 6.93 (1H, m), 6.95 (1H, dd), 7.03 (1H, d), 7.31 (1H, t), 7.62 - 7.65 (1H, m), 8.32 - 8.51 (2H, m), 8.95 (1H, t)	Example 2 step c
593 (I)	536 (M+H)		(DMSO-D6) δ 1.42 - 1.63 (4H, m), 1.66 (1H, d), 1.84 (1H, d), 1.89 - 1.97 (2H, m), 2.32 - 2.45 (1H, m), 2.50 - 2.61 (2H, m), 2.72 - 2.87 (3H, m), 3.08 (1H, t), 3.37 (3H, s), 3.48 (1H, d), 4.37 - 4.46 (1H, m), 4.46 - 4.55 (1H, m), 6.98 (1H, dd), 7.25 (1H, d), 7.49 (1H, d), 8.21 (1H, t), 8.30 (1H, t), 8.48 (1H, t)	Example 2 step c
594 (I)	550 (M+H)		(DMSO-D6) δ 1.38 - 1.52 (2H, m), 1.53 - 1.64 (2H, m), 1.84 (2H, d), 1.88 - 1.98 (2H, m), 2.37 - 2.45 (4H, m), 2.58 - 2.68 (1H, m), 2.74 - 2.82 (3H, m), 3.17 (3H, s), 4.37 - 4.50 (2H, m), 6.99 (1H, dd), 7.00 -	Example 2 step c

			7.02 (1H, m), 7.26 (1H, d), 7.49 (1H, d), 7.61 (1H, d), 7.70 (1H, dd), 8.23 (1H, d)	
299 (IV)	525 (M+H)		(DMSO-D6) δ 1.38 – 1.5 (2H, m), 1.60 – 1.70 (2H, m), 1.81 – 2.00 (2H, m), 2.40 (3H, s), 2.41 – 3.31 (9H, m), 3.35 (3H, s), 3.41 – 3.58 (1H, m), 4.4 – 4.55 (2H, m), 7.09 (1H, d), 7.34 (1H, d), 7.71 (2H, m), 7.90 (1H, s), 8.0 (1H, m)	Example 12
300 (IV)	489 (M+H)		(DMSO-D6) δ 1.10 (3H, t), 1.35 – 1.50 (2H, m), 1.58 – 1.70 (2H, m), 1.81 – 1.97 (2H, m), 2.25 – 3.20 (11H, m), 3.32 (3H, s), 3.4 – 3.6 (1H, m), 4.25 – 4.6 (2H, m), 6.85 – 7.00 (3H, m), 7.63 – 7.78 (2H, m), 7.90 (1H, s), 7.98 – 8.02 (1H, m)	Example 12
143 (IV)	465 (M+H)		($CDCl_3$) δ 1.63 - 1.74 (2H, m), 1.78 - 1.88 (3H, m), 1.92 - 2.04 (3H, m), 2.19 (3H, s), 2.43 - 2.55 (2H, m), 2.64 (1H, tt), 2.76 – 2.94 (3H, m), 3.13 - 3.27 (1H, m), 4.25 - 4.35 (2H, m), 4.82 – 4.90 (1H, m), 6.74 (1H, d), 7.07 (1H, dd), 7.11 (1H, d), 7.56 (1H, dd), 7.85 (1H, d), 8.25 (1H, dd), 8.32 (1H, d), 9.19 (1H, dd)	Example 2 step c
301 (IV)	530 (M+H)		($CDCl_3$) δ 1.57 - 1.71 (2H, m), 1.80 - 1.91 (3H, m), 1.95 - 2.06 (3H, m), 2.20 (3H, s), 2.47 - 2.55 (2H, m), 2.61 - 2.72 (1H, m), 2.79 - 2.86 (2H, m), 2.91 - 3.35 (2H, m), 3.08 (3H, s), 4.28 – 4.37 (1H, m), 4.69 - 4.80 (2H, m), 6.74 (1H, d), 6.90 (1H, d), 7.07 (1H, dd), 7.12 (1H, d), 7.57 (1H, d), 7.79 (1H, dd), 8.32 (1H, d)	Example 2 step c

572 (I)	500 (M+H)		($CDCl_3$) δ 1.37 - 1.66 (2H, m), 1.73 - 1.88 (3H, m), 1.93 - 2.05 (3H, m), 2.41 - 2.51 (2H, m), 2.52 - 2.63 (1H, m), 2.75 - 2.86 (2H, m), 2.86 - 3.09 (2H, m), 3.71 - 3.90 (1H, m), 4.23 - 4.32 (1H, m), 4.77 - 4.93 (1H, m), 6.75 (1H, dd), 6.99 (1H, d), 7.27 – 7.32 (3H, m), 7.54 - 7.67 (1H, m), 7.57 (1H, t), 7.74 (1H, t), 8.46 (1H, d)	Example 2 step c
120 (IV)	480 (M+H)		($CDCl_3$) δ 1.46 - 1.66 (2H, m), 1.79 - 2.01 (6H, m), 2.19 (3H, s), 2.45 - 2.52 (2H, m), 2.59 (1H, tt), 2.75 - 2.84 (2H, m), 2.92 – 3.20 (2H, m), 3.74 - 4.00 (1H, m), 4.27 - 4.35 (1H, m), 4.55 – 4.90 (1H, m), 6.49 (1H, dd), 6.74 (1H, d), 7.07 (1H, dd), 7.11 (1H, d), 7.76 (1H, d), 7.88 (1H, dd), 8.03 (1H, d), 8.48 (1H, d), 8.57 (1H, d)	Example 2 step c using acid available from Bionet Research Ltd., Highfield Industrial Estate, Camelford, Cornwall, PL32 9QZ, United Kingdom
145 (IV)	538 (M+H)		($CDCl_3$) δ 1.35 - 1.73 (2H, m), 1.77 - 1.89 (3H, m), 1.92 - 2.06 (3H, m), 2.19 (3H, s), 2.43 - 2.64 (3H, m), 2.74 - 2.83 (2H, m), 2.83 - 2.94 (1H, m), 3.00 - 3.12 (1H, m), 3.38 - 3.54 (1H, m), 4.26 - 4.35 (1H, m), 4.76 - 4.92 (1H, m), 6.73 (1H, d), 7.07 (1H, dd), 7.11 (1H, d), 7.70 (1H, d), 7.98 (1H, dd), 8.19 (1H, d)	Example 2 step c using acid available from Peakdale Inc. 109 East Scotland Drive Bear, DE, 19701-1756 USA
240 (IV)	465 (M+H)		($CDCl_3$) δ 1.62 - 1.74 (2H, m), 1.77 - 1.86 (3H, m), 1.93 - 2.03 (3H, m), 2.33 (3H, s), 2.41 - 2.54 (2H, m), 2.65 (1H, tt), 2.78 – 2.86 (1H, m), 2.89 (2H, td), 3.21 (1H, td), 4.21 - 4.35 (2H, m), 4.81 - 4.90 (1H, m), 6.67 (1H, dd), 6.78 (1H, d), 7.20 (1H, d), 7.57 (1H, dd), 7.85 (1H, d), 8.25 (1H, dd), 8.32 (1H, d), 9.19 (1H, dd)	Example 2 step c

267 (IV)	453 (M+H)		($CDCl_3$) δ 1.62 (2H, qd), 1.79 - 2.01 (6H, m), 2.19 (3H, s), 2.43 - 2.52 (2H, m), 2.64 (1H, tt), 2.74 - 2.85 (2H, m), 3.12 - 3.22 (1H, m), 4.26 - 4.32 (1H, m), 4.77 - 4.86 (1H, m), 5.24 - 5.33 (1H, m), 6.74 (1H, d), 6.84 (1H, td), 7.07 (1H, dd), 7.11 (1H, d), 7.21 (1H, dd), 7.23 (1H, dd), 7.60 (1H, dd), 8.06 (1H, d), 8.13 (1H, dt)	Example 2 step c
199 (IV)	470 (M+H)		($CDCl_3$) δ 1.57 - 1.67 (2H, m), 1.81 - 1.88 (2H, m), 1.93 - 2.01 (4H, m), 2.20 (3H, s), 2.50 (2H, td), 2.65 (1H, tt), 2.82 (2H, td), 2.96 - 3.20 (2H, m), 4.28 - 4.35 (1H, m), 4.74 (2H, d), 6.73 – 6.75 (2H, m), 7.01 - 7.12 (3H, m), 7.28 (1H, d), 7.35 (1H, dd), 9.35 (1H, s)	Example 2 step c
181 (IV)	538 (M+H)		($CDCl_3$) δ 1.50 - 1.65 (2H, m), 1.70 - 1.83 (3H, m), 1.93 - 2.04 (3H, m), 2.32 (3H, s), 2.40 - 2.50 (2H, m), 2.52 - 2.62 (1H, m), 2.76 - 2.92 (3H, m), 3.01 - 3.10 (1H, m), 3.38 - 3.52 (1H, m), 4.22 - 4.30 (1H, m), 4.77 - 4.90 (1H, m), 6.67 (1H, dd), 6.77 (1H, d), 7.20 (1H, d), 7.70 (1H, d), 7.98 (1H, dd), 8.19 (1H, d)	Example 2 step c
216 (IV)	526 (M+H)		($CDCl_3$) δ 1.47 - 1.66 (2H, m), 1.79 - 1.88 (3H, m), 1.95 - 2.04 (3H, m), 2.32 (3H, s), 2.53 - 2.61 (2H, m), 2.70 (1H, tt), 2.76 – 2.89 (3H, m), 2.99 - 3.13 (1H, m), 3.63 - 3.74 (1H, m), 4.27 – 4.33 (1H, m), 4.63 - 4.77 (1H, m), 6.67 (1H, dd), 6.77 (1H, d), 7.20 (1H, d), 7.50 (1H, dd), 7.56 (1H, d), 8.09 (1H, d)	Example 2 step c

266 (IV)	480 (M+H)		($CDCl_3$) δ 1.37 - 1.67 (2H, m), 1.76 - 1.85 (3H, m), 1.93 - 2.01 (3H, m), 2.32 (3H, s), 2.41 - 2.48 (2H, m), 2.50 - 2.60 (1H, m), 2.77 - 2.85 (2H, m), 2.86 - 3.10 (2H, m), 3.73 - 3.85 (1H, m), 4.23 - 4.29 (1H, m), 4.77 - 4.92 (1H, m), 6.67 (1H, dd), 6.77 (1H, d), 7.20 (1H, d), 7.21 - 7.31 (1H, m), 7.54 - 7.68 (1H, m), 7.56 (2H, t), 7.73 (1H, t), 8.46 (1H, d)	Example 2 step c
540 (I)	485 (M+H)		($CDCl_3$) δ 1.69 - 1.84 (4H, m), 1.95 - 2.02 (4H, m), 2.43 - 2.53 (2H, m), 2.65 (1H, tt), 2.79 - 2.93 (3H, m), 3.18 - 3.25 (1H, m), 4.23 - 4.35 (2H, m), 4.82 - 4.90 (1H, m), 6.75 (1H, dd), 7.00 (1H, d), 7.31 (1H, d), 7.57 (1H, dd), 7.86 (1H, d), 8.25 (1H, dd), 8.32 (1H, d), 9.19 (1H, dd)	Example 2 step c
204 (IV)	470 (M+H)		($CDCl_3$) δ 1.57 - 1.67 (2H, m), 1.77 - 1.85 (2H, m), 1.94 - 2.02 (4H, m), 2.33 (3H, s), 2.45 - 2.52 (2H, m), 2.61 - 2.69 (1H, m), 2.81 - 2.86 (2H, m), 2.97 - 3.18 (2H, m), 4.24 - 4.30 (1H, m), 4.74 (2H, d), 6.68 (1H, dd), 6.73 (1H, d), 6.78 (1H, d), 7.04 (1H, td), 7.20 (1H, d), 7.28 (1H, d), 7.35 (1H, dd), 9.34 (1H, s).	Example 2 step c
104 (IV)	480 (M+H)		($CDCl_3$) δ 1.49 - 1.63 (2H, m), 1.76 - 2.00 (6H, m), 2.33 (3H, s), 2.43 - 2.49 (2H, m), 2.59 (1H, tt), 2.79 - 2.85 (3H, m), 3.00 – 3.18 (1H, m), 3.81 - 3.96 (1H, m), 4.24 - 4.29 (1H, m), 4.67 – 4.83 (1H, m), 6.49 (1H, dd), 6.67 (1H, dd), 6.78 (1H, d), 7.20 (1H, d),,7.76 (1H, d), 7.88 (1H, dd), 8.03 (1H, d), 8.48 (1H, d), 8.57 (1H, d)	Example 2 step c

243 (IV)	486 (M+H)		(DMSO-D6/$CDCl_3$) δ 1.43 - 1.59 (2H, m), 1.73 - 1.98 (6H, m), 2.32 (3H, s), 2.43 - 2.48 (2H, m), 2.79 - 2.87 (2H, m), 2.91 – 3.40 (5H, m), 4.23 - 4.30 (1H, m), 6.68 (1H, dd), 6.78 (1H, d), 7.14 (1H, d), 7.19 (1H, d), 7.26 (1H, dd), 7.43 (1H, d), 7.51 (1H, s).	Example 2 step c
191 (IV)	514 (M+H)		($CDCl_3$) δ 1.46 - 1.59 (2H, m), 1.76 - 2.00 (6H, m), 2.32 (3H, s), 2.44 - 2.48 (2H, m), 2.54 - 2.59 (1H, m), 2.78 - 2.85 (3H, m), 3.42 (3H, s), 3.45 (3H, s), 3.79 - 3.92 (1H, m), 4.23 - 4.30 (1H, m), 4.67 - 4.79 (1H, m), 6.67 (1H, dd), 6.77 (1H, d), 7.02 (1H, d), 7.15 (1H, s), 7.20 (1H, d), 7.37 (1H, d)	Example 2 step c
519 (I)	490 (M+H)		($CDCl_3$) δ 1.61 (2H, qd), 1.77 - 1.85 (2H, m), 1.94 - 2.02 (4H, m), 2.38 - 2.51 (2H, m), 2.65 (1H, tt), 2.80 - 2.85 (2H, m), 2.95 - 3.14 (2H, m), 4.25 - 4.30 (1H, m), 4.73 - 4.77 (2H, m), 6.73 (1H, d), 6.75 (1H, dd), 7.00 (1H, d), 7.03 (1H, td), 7.27 (1H, dd), 7.31 (1H, d), 7.35 (1H, dd), 9.49 (1H, s)	Example 2 step c
494 (I)	558 (M+H)		($CDCl_3$) δ 1.48 - 1.71 (2H, m), 1.74 - 1.83 (3H, m), 1.93 - 2.03 (3H, m), 2.42 - 2.50 (2H, m), 2.55 - 2.62 (1H, m), 2.76 - 2.93 (3H, m), 3.01 - 3.10 (1H, m), 3.40 - 3.50 (1H, m), 4.22 - 4.31 (1H, m), 4.77 - 4.90 (1H, m), 6.75 (1H, dd), 6.98 (1H, d), 7.30 (1H, d), 7.67 (1H, d), 7.98 (1H, dd), 8.19 (1H, d)	Example 2 step c

238 (IV)	511 (M+H)	172-173	($CDCl_3$) δ 1.53 - 1.63 (2H, m), 1.82 - 1.89 (3H, m), 2.00 - 2.05 (3H, m), 2.05 - 2.61 (3H, m), 2.80 - 2.84 (3H, m), 2.98 - 3.09 (1H, m), 3.03 (3H, s), 3.77 (1H, br s), 4.41 - 4.45 (1H, m), 4.70 (1H, br s), 6.99 (2H, d), 7.21 - 7.26 (1H, m), 7.44 - 7.54 (2H, m), 7.86 (2H, d)	Example 21
496 (I)	500 (M+H)		(DMSO-D6) δ 1.46 (2H, qd), 1.54 - 1.61 (2H, m), 1.65 - 1.88 (3H, m), 1.89 - 1.97 (2H, m), 2.37 - 2.42 (2H, m), 2.54 - 2.61 (1H, m), 2.73 - 2.83 (2H, m), 3.04 - 3.17 (1H, m), 3.61 - 3.72 (1H, m), 4.39 - 4.56 (2H, m), 6.62 (1H, dd), 6.98 (1H, dd), 7.25 (1H, d), 7.49 (1H, d), 7.87 (1H, dd), 7.97 (1H, dd), 8.04 (1H, dd), 8.52 (1H, dd), 8.65 (1H, dd)	Example 2 step c
483 (I)	506 (M+H)		(DMSO-D6) δ 1.41 (2H, qd), 1.53 - 1.62 (2H, m), 1.68 - 1.82 (2H, m), 1.89 - 1.96 (2H, m), 2.36 - 2.43 (3H, m), 2.53 - 2.59 (3H, m), 2.74 - 2.80 (3H, m), 4.39 - 4.45 (1H, m), 6.97 (1H, dd), 7.13 (1H, d), 7.25 (1H, d), 7.30 (1H, dd), 7.49 (1H, d), 7.66 (1H, d)	Example 2 step c
302 (IV)	498 (M+H)		($CDCl_3$) δ 1.40 - 1.74 (2H, m), 1.79 - 2.02 (6H, m), 2.20 (3H, s), 2.42 - 2.61 (3H, m), 2.67 (1H, td), 2.74 - 2.84 (2H, m), 3.16 (1H, t), 3.91 - 4.00 (1H, m), 4.26 - 4.36 (1H, m), 4.58 - 4.78 (5H, m), 6.74 (1H, d), 6.76 - 6.79 (1H, m), 6.98 - 7.02 (3H, m), 7.07 (1H, dd), 7.12 (1H, d)	Example 2 step c
303 (IV)	498 (M+H)		($CDCl_3$) δ 1.42 - 1.61 (2H, m), 1.77 - 1.90 (3H, m), 1.93 - 2.03 (3H, m), 2.33 (3H, s), 2.41 - 2.49 (2H, m), 2.57 (1H, tt), 2.67 (1H, t), 2.77 - 2.84 (2H, m), 3.16 (1H, t), 3.95 (1H, d), 4.24 – 4.29 (1H, m), 4.59 -	Example 2 step c

			4.77 (5H, m), 6.68 (1H, dd), 6.75 - 6.79 (2H, m), 6.97 - 7.00 (3H, m), 7.21 (1H, d)	
596 (I)	518 (M+H)		($CDCl_3$) δ 1.43 - 1.64 (2H, m), 1.77 - 1.89 (3H, m), 1.94 - 2.01 (3H, m), 2.41 - 2.50 (2H, m), 2.57 (1H, tt), 2.68 (1H, t), 2.76 – 2.83 (2H, m), 3.16 (1H, t), 3.94 - 3.97 (1H, m), 4.24 - 4.30 (1H, m), 4.58 - 4.63 (1H, m), 4.68 (2H, s), 4.76 (2H, d), 6.76 - 6.78 (2H, m), 6.98 - 7.00 (3H, m), 7.26 (1H, s), 7.31 (1H, d)	Example 2 step c
467 (I)	534 (M+H)		(DMSO-D6) δ 1.35 - 1.50 (2H, m), 1.52 - 1.65 (3H, m), 1.68 – 1.84 (2H, m), 1.88 - 1.98 (2H, m), 2.35 - 2.44 (2H, m), 2.54 – 2.61 (1H, m), 2.73 - 2.82 (3H, m), 3.37 (3H, s), 3.57 (2H, s), 3.60 - 3.71 (1H, m), 4.38 - 4.56 (2H, m), 6.98 (1H, dd), 7.07 (1H, dd), 7.24 (1H, d), 7.26 (1H, d), 7.47 (1H, d), 7.50 (1H, d)	Example 2 step c
269 (IV)	453 (M+H)		($CDCl_3$) δ 1.55 - 1.68 (4H, m), 1.75 - 2.01 (4H, m), 2.33 (3H, s), 2.41 - 2.51 (2H, m), 2.64 (1H, tt), 2.78 - 2.87 (3H, m), 3.12 – 3.24 (1H, m), 4.21 - 4.29 (1H, m), 4.76 - 4.88 (1H, m), 5.23 – 5.34 (1H, m), 6.67 (1H, dd), 6.78 (1H, d), 6.84 (1H, t), 7.19 – 7.26 (2H, m), 7.60 (1H, d), 8.06 (1H, s), 8.13 (1H, dd)	Example 2 step c
597 (I)	546 (M+H)		($CDCl_3$) δ 1.39 - 1.66 (2H, m), 1.73 - 1.86 (4H, m), 1.92 - 2.03 (2H, m), 2.41 - 2.50 (2H, m), 2.53 - 2.63 (1H, m), 2.76 - 2.88 (2H, m), 2.98 - 3.12 (1H, m), 3.62 - 3.77 (1H, m), 4.24 - 4.29 (1H, m), 4.62 - 4.78 (1H,	Example 2 step c

			m), 6.75 (1H, dd), 6.99 (1H, d), 7.31 (2H, d), 7.53 (1H, dd), 7.57 (1H, t), 8.12 (1H, d)	
598 (I)	474 (M+H)		($CDCl_3$) δ 1.58 - 1.75 (2H, m), 1.80 - 1.88 (2H, m), 1.91 - 2.05 (4H, m), 2.53 - 2.61 (2H, m), 2.71 - 2.90 (4H, m), 3.18 - 3.22 (1H, m), 4.27 - 4.33 (1H, m), 4.84 (1H, d), 5.55 (1H, d), 6.75 (1H, dd), 6.95 (1H, dd), 7.00 (1H, d), 7.31 (1H, d), 8.09 (1H, s), 8.46 (1H, dd), 8.62 (1H, dd)	Example 2 step c
579 (I)	491 (M+H)		($CDCl_3$) δ 1.61 (1H, qd), 1.75 - 2.02 (7H, m), 2.42 - 2.51 (2H, m), 2.59 - 2.67 (1H, m), 2.75 - 2.86 (3H, m), 3.12 - 3.21 (1H, m), 4.23 - 4.29 (1H, m), 4.76 - 4.85 (1H, m), 5.23 - 5.32 (1H, m), 6.75 (1H, dd), 6.99 (1H, d), 7.16 (1H, ddd), 7.30 (1H, d), 7.58 (1H, dd), 8.07 (2H, s)	Example 2 step c
599 (I)	487 (M+H)		($CDCl_3$) δ 1.58 - 1.67 (1H, m), 1.75 - 2.02 (7H, m), 2.43 - 2.51 (3H, m), 2.59 - 2.68 (1H, m), 2.61 (3H, s), 2.76 - 2.85 (3H, m), 3.12 - 3.23 (1H, m), 4.23 - 4.28 (1H, m), 4.78 - 4.87 (1H, m), 5.30 - 5.38 (1H, m), 6.67 (1H, d), 6.75 (1H, dd), 7.20 (1H, dd), 7.30 (1H, d), 7.51 (1H, d), 8.01 (1H, s)	Example 2 step c
600 (I)	507 (M+H)		($CDCl_3$) δ 1.61 (1H, qd), 1.70 - 2.04 (7H, m), 2.41 - 2.53 (2H, m), 2.63 (1H, t), 2.73 - 2.88 (3H, m), 3.09 - 3.23 (1H, m), 4.21 – 4.31 (1H, m), 4.74 - 4.86 (1H, m), 5.20 - 5.30 (1H, m), 6.75 (1H, dd), 6.99 (1H, d), 7.19 (1H, d), 7.30 (1H, d), 7.55 (1H, d), 8.04 (1H, s), 8.19 (1H, s)	Example 2 step c

304 (IV)	505 (M+H)		($CDCl_3$) δ 1.57 - 1.68 (2H, m), 1.82 - 2.01 (6H, m), 2.46 - 2.54 (2H, m), 2.46 (3H, s), 2.59 - 2.69 (1H, m), 2.73 - 2.90 (3H, m), 3.10 - 3.23 (1H, m), 4.32 - 4.39 (1H, m), 4.76 - 4.85 (1H, m), 5.22 - 5.32 (1H, m), 6.75 (1H, d), 7.14 - 7.27 (2H, m), 7.58 (1H, dd), 8.07 (2H, s)	Example 2 step c
601 (I)	487 (M+H)		($CDCl_3$) δ 1.55 - 1.65 (1H, m), 1.75 - 2.01 (7H, m), 2.40 (3H, s), 2.44 - 2.50 (2H, m), 2.63 (1H, qt), 2.73 - 2.86 (3H, m), 3.10 – 3.22 (1H, m), 4.22 - 4.28 (1H, m), 4.75 - 4.86 (1H, m), 5.22 – 5.34 (1H, m), 6.66 (1H, dd), 6.75 (1H, dd), 6.99 (1H, d), 7.30 (1H, d), 7.34 (1H, s), 7.97 (1H, s), 7.99 (1H, d)	Example 2 step c
343 (I)	566 (M+H)		($CDCl_3$) δ 1.39 - 1.65 (1H, m), 1.77 - 1.89 (4H, m), 1.94 - 2.03 (3H, m), 2.43 - 2.50 (2H, m), 2.54 - 2.62 (1H, m), 2.77 - 2.90 (3H, m), 3.03 - 3.13 (1H, m), 3.53 (3H, s), 3.65 - 3.74 (1H, m), 4.26 - 4.31 (1H, m), 4.26 (2H, s), 4.69 - 4.79 (1H, m), 6.75 (1H, dd), 6.99 (1H, d), 7.26 - 7.35 (3H, m), 8.00 (1H, d)	Example 2 step c
603 (I)	526 (M+H)		($CDCl_3$) δ 1.49 - 1.58 (2H, m), 1.76 - 1.84 (3H, m), 1.90 - 2.01 (4H, m), 2.44 - 2.48 (2H, m), 2.53 - 2.59 (1H, m), 2.78 - 2.82 (2H, m), 2.78 - 3.00 (5H, m), 3.15 - 3.19 (1H, m), 4.24 - 4.29 (1H, m), 4.96 (2H, s), 6.74 - 6.80 (2H, m), 6.99 (1H, d), 7.31 (1H, d), 7.66 - 7.70 (2H, m)	Example 2 step c
534 (I)	543 (M+H)		($CDCl_3$) δ 1.49 (3H, t), 1.57 - 2.00 (6H, m), 2.43 - 2.52 (2H, m), 2.56 - 2.62 (3H, m), 2.67 (3H, s), 2.78 - 2.84 (3H, m), 3.10 – 3.19 (1H, m),	Example 2 step c

			3.74 (1H, d), 4.25 (1H, dquintet), 4.42 - 4.49 (2H, m), 4.76 (1H, d), 6.75 (1H, dd), 6.99 (1H, d), 7.23 (1H, d), 7.30 (1H, d), 8.09 (1H, s), 8.60 (1H, d)	
5 (II)	474 (M+H)			Example 2 step c
6 (II)	468 (M+H)		(DMSO-D6) δ 1.39 - 1.45 (1H, m), 1.54 - 1.93 (6H, m), 2.32 – 2.39 (2H, m), 2.49 - 2.53 (2H, m), 2.72 - 3.02 (4H, m), 3.29 – 3.32 (2H, m), 4.31 - 4.34 (1H, m), 6.75 - 6.79 (1H, m), 7.08 (1H, ddd), 7.30 (2H, dt), 7.49 - 7.56 (2H, m), 7.76 (1H, t), 8.24 (1H, dd)	Example 2 step c
7 (II)	453 (M+H)		(DMSO-D6) δ 1.45 - 1.69 (5H, m), 1.84 - 1.99 (3H, m), 2.40 (2H, t), 2.59 - 2.66 (1H, m), 2.73 - 2.92 (3H, m), 3.03 - 3.14 (1H, m), 3.69 - 3.76 (1H, m), 4.31 - 4.37 (1H, m), 4.55 - 4.61 (1H, m), 6.78 (1H, dd), 7.09 (1H, ddd), 7.31 (1H, dt), 7.69 – 7.78 (2H, m), 8.49 - 8.65 (2H, m), 9.15 (1H, dd)	Example 2 step c
8 (II)	441 (M+H)		(DMSO-D6) δ 1.34 - 1.45 (2H, m), 1.52 - 1.61 (2H, m), 1.76 – 1.86 (2H, m), 1.87 - 1.96 (2H, m), 2.33 - 2.44 (2H, m), 2.56 – 2.63 (1H, m), 2.72 - 2.81 (3H, m), 3.05 - 3.14 (1H, m), 4.29 – 4.38 (1H, m), 4.51 - 4.61 (1H, m), 5.09 - 5.19 (1H, m), 6.73 – 6.79 (1H, m), 6.94 - 6.99 (1H, m), 7.04 - 7.12 (1H, m), 7.28 – 7.34 (2H, m), 7.61 (1H, dd), 8.30 (1H, s), 8.56 (1H, dt)	Example 2 step c

305 (IV)	514 (M+H)		(DMSO-D6) δ 1.42 - 1.51 (2H, m), 1.60 - 1.93 (6H, m), 2.41 – 2.47 (2H, m), 2.41 (3H, s), 2.54 - 2.60 (1H, m), 2.72 - 2.80 (2H, m), 3.05 - 3.15 (1H, m), 3.29 - 3.35 (1H, m), 3.60 - 3.71 (1H, m), 4.44 - 4.54 (2H, m), 6.59 - 6.64 (1H, m), 7.07 - 7.13 (1H, m), 7.31 - 7.38 (1H, m), 7.86 - 7.89 (1H, m), 7.95 - 7.99 (1H, m), 8.01 - 8.07 (1H, m), 8.50 - 8.54 (1H, m), 8.63 - 8.67 (1H, m)	Example 2 step c
306 (IV)	531 (M+H)		(DMSO-D6) δ 1.39 - 1.95 (8H, m), 2.40 (3H, s), 2.42 - 2.47 (2H, m), 2.55 - 2.63 (2H, m), 2.72 - 2.81 (2H, m), 2.94 - 3.09 (2H, m), 3.42 (3H, s), 4.14 - 4.32 (1H, m), 4.46 - 4.54 (1H, m), 7.10 (1H, d), 7.36 (1H, d), 7.49 (1H, d), 7.78 (1H, d)	Example 2 step c
307 (IV)	525 (M+H)		(DMSO-D6) δ 1.39 – 1.95 (9H, m), 2.42 (3H, s), 2.44 – 2.48 (1H, m), 2.55 – 2.61 (1H, m), 2.70 – 2.83 (2H, m), 2.99 – 3.10 (1H, m), 3.29 (3H, s), 3.41 – 3.52 (2H, m), 4.46 – 4.58 (2H, m), 7.11 (1H, d), 7.36 (1H, d), 7.66 (2H, dd), 7.99 (2H, dd)	Example 2 step c
308 (IV)	512 (M+H)		(DMSO-D6) δ 1.60-4.25 (18H, m), 4.55-4.80 (1H, m), 5.22-5.45 (1H, m), 7.05 (1H, t), 7.75-7.82 (2H,m), 7.85 (1H, s), 8.00-8.18(2H, m), 8.60 (1H, s), 9.63 (1H, br s)	Prepared in a similar manner to Example 15 and isolated as the trifluoroacetate salt
1 (V)	509 (M+H)	87-88	(DMSO-D^6) δ 1.11 - 1.18 (2H, m), 1.36 - 1.53 (4H, m), 1.63 – 1.78 (2H, m), 2.07 (2H, t), 2.48 - 2.52 (2H, m), 2.81 - 2.84 (4H, m), 3.01 - 3.04 (2H, m), 3.27 - 3.27 (3H, m), 3.49 - 3.50 (1H, m), 4.44 - 4.53 (1H,	Example 2 step c

			m), 7.15 - 7.18 (1H, m), 7.44 - 7.45 (1H, m), 7.50 - 7.53 (1H, m), 7.69 - 7.76 (2H, m), 7.90 (1H, t), 7.98 – 8.02 (1H, m)	
2 (V)	510 (M+H)		($CDCl_3$) δ 1.38 - 1.48 (3H, m), 1.59 (1H, br s), 1.81 - 2.07 (4H, m), 2.34 (2H, t), 2.55 - 2.60 (1H, m), 2.84 - 2.92 (3H, m), 3.07 (4H, s), 3.21 (1H, br s), 3.60 (1H, d), 3.68 (1H, br s), 4.74 (1H, br s), 6.41 (1H, dd), 6.64 (1H, d), 7.16 (1H, d), 7.62 - 7.70 (2H, m), 7.97 - 8.02 (2H, m)	Example 12
3 (V)	523 (M+H)		(DMSO-D6) δ 1.42 - 1.56 (4H, m), 1.64 - 1.86 (4H, m), 2.33 (2H, t), 2.54 - 2.61 (1H, m), 2.76 - 2.85 (1H, m), 2.87 - 2.93 (2H, m), 3.04 - 3.12 (1H, m), 3.28 (3H, s), 3.36 - 3.44 (1H, m), 3.48 - 3.57 (1H, m), 4.47 - 4.55 (1H, m), 7.70 - 7.77 (2H, m), 7.80 (1H, d), 7.91 - 7.95 (2H, m), 8.00 (1H, dt), 8.14 - 8.16 (1H, m)	Prepared in a similar maner to Example 12 using (3,4-Dichloro-phenyl)-piperidin-4-yl-methanone hydrochloride (free base was made insitu using triethylamine
310 (IV)	478 (M+H)	169-170	(DMSO-D6) δ 1.29 - 1.40 (2H, m), 1.53 - 1.62 (2H, m), 1.71 – 1.77 (2H, m), 1.89 - 1.96 (2H, m), 2.35 - 2.42 (2H, m), 2.45 – 2.49 (1H, m), 2.68 - 2.79 (4H, m), 3.70 (3H, s), 4.10 - 4.17 (2H, m), 4.38 - 4.45 (1H, m), 6.78 - 6.82 (2H, m), 6.98 (1H, dd), 7.25 (1H, d), 7.30 - 7.34 (2H, m), 7.49 (1H, d), 8.30 (1H, s)	Example 26 using 4-Methoxyphenylisocyanate
311 (IV)	466 (M+H)	217	(DMSO-D6) δ 1.29 - 1.40 (2H, m), 1.53 - 1.62 (2H, m), 1.72 – 1.78 (2H, m), 1.89 - 1.96 (2H, m), 2.36 - 2.42 (2H, m), 2.44 – 2.49 (1H, m), 2.71 - 2.79 (4H, m), 4.11 - 4.17 (2H, m), 4.38 – 4.45 (1H, m), 6.98 (1H,dd), 7.05 (2H,t), 7.25 (1H,d), 7.45 (2H,tt), 7.49 (1H,d), 8.50 (1H,s)	Example 26 using 4-Fluorophenylisocyanate

312 (IV)	494 (M+H)	170-172	(DMSO-D6) δ 1.29 - 1.40 (2H, m), 1.52 - 1.62 (2H, m), 1.72 – 1.78 (2H, m), 1.89 - 1.96 (2H, m), 2.36 - 2.42 (2H, m), 2.43 (3H, s), 2.44 - 2.48 (1H, m), 2.71 - 2.79 (4H, m), 4.15 (2H, d), 4.38 - 4.45 (1H, m), 6.81 (1H, d), 6.98 (1H, dd), 7.15 (1H, t), 7.24 - 7.27 (2H, m), 7.43 (1H, t), 7.49 (1H, d), 8.48 (1H, s)	Example 26 using 3-(Methylthio)phenylisocyanate
313 (IV)	462 (M+H)	178-179	(DMSO-D6) δ 1.22 - 1.34 (2H, m), 1.52 - 1.61 (2H, m), 1.65 – 1.72 (2H, m), 1.88 - 1.95 (2H, m), 2.33 - 2.46 (3H, m), 2.61 – 2.76 (4H, m), 3.99 - 4.05 (2H, m), 4.22 (2H, d), 4.37 - 4.44 (1H, m), 6.97 (1H, dd), 7.04 (1H, t), 7.18 - 7.31 (6H, m), 7.49 (1H, d)	Example 26 using Benzylisocyanate
314 (IV)	492 (M+H)	166-167	(DMSO-D6) δ 1.21 - 1.32 (2H, m), 1.51 - 1.61 (2H, m), 1.64 – 1.71 (2H, m), 1.88 - 1.95 (2H, m), 2.32 - 2.46 (3H, m), 2.59 – 2.67 (2H, m), 2.69 - 2.76 (2H, m), 3.71 (3H, s), 4.01 (2H, d), 4.14 (2H, d), 4.37 - 4.44 (1H, m), 6.83 - 6.87 (2H, m), 6.94 – 6.99 (2H, m), 7.14 - 7.18 (2H, m), 7.25 (1H, d), 7.49 (1H, d)	Example 26 using 4-Methoxybenzylisocyanate
315 (IV)	480 (M+H)	209-210	(DMSO-D6) δ 1.21 - 1.32 (2H, m), 1.52 - 1.61 (2H, m), 1.65 – 1.71 (2H, m), 1.88 - 1.95 (2H, m), 2.32 - 2.46 (3H, m), 2.60 – 2.68 (2H, m), 2.70 - 2.76 (2H, m), 4.01 (2H, d), 4.19 (2H, d), 4.38 - 4.44 (1H, m), 6.97 (1H, dd), 7.05 (1H, t), 7.11 (2H, t), 7.24 - 7.29 (3H, m), 7.49 (1H, d)	Example 26 using 4-Fluorobenzylisocyanate

MS = Mass Spectrum has been obtained using either APCI+ or ES+ or ES-

The preparations of certain intermediates are now presented.

Method A

1-(3-Methoxy-4-nitro-benzoyl)-piperidin-4-one

CDI (9g) added to a solution of 3-methoxy-4-nitrobenzoic acid (10g) stirring in THF (200ml) at RT. After 1 hour, 4-piperidone hydrochloride (6.9g) and triethylamine (7.8ml) were added and the mixture stirred overnight. The mixture was diluted with ethyl acetate, washed with 2N HCl (100ml) then saturated $NaHCO_3$ solution (200ml) then saturated brine (200ml). The organic layer was dried ($MgSO_4$) and evaporated to leave a residue which was purified by column chromatography (silica, mixtures of MeOH in dichloromethane) to give the product as a yellow solid (8.5g; MS: APCI$^+$(M+H) 279).

Method B

1-(3-Methanesulfonyl-benzoyl)-piperidin-4-one

PyBrOP™ (17.3g) was added to a stirred mixture of 3-methanesulphonyl benzoic acid (7.35g), 4-piperidone hydrochloride (5g) and Hunig's base (25ml) in dichloromethane (250ml) with stirring at RT. The mixture was stirred overnight then washed with saturated $NaHCO_3$ solution (200ml) and then with saturated brine (200ml). The organic layer was evaporated and the resulting residue purified by column chromatography (silica, 1:1 ethyl acetate: dichloromethane) to give the product as a thick oil (9.6g; MS: APCI$^+$(M+H) 282).

Method C

1-(Benzo[1,2,3]thiadiazole-5-carbonyl)-piperidin-4-one

CDI (4.5g) added to a solution of the benzo[1,2,3]thiadiazole-5-carboxylic acid (5g) stirring in THF (100ml) at RT. After 1hour 4-piperidone hydrochloride (3.7g) and triethylamine (4.3ml) were added and the mixture stirred overnight. The resulting mixture was diluted with ethyl acetate, washed with 2M HCl (100ml), saturated $NaHCO_3$ solution (200ml) and then with saturated brine (200ml). The organic layer was dried ($MgSO_4$) and evaporated to leave a residue which was purified by column chromatography (silica, eluting with mixtures of ethyl acetate in dichloromethane) to give the product as a yellow oil (2.1g; MS: APCI$^+$(M+H)262).

Method D

[1,4']Bipiperidinyl-4-ol

4-Oxo-piperidine-1-carboxylic acid tert-butyl ester (20g) and 4-hydroxypiperidine (6.7g) were stirred together in dichloroethane (200ml) with acetic acid (4ml) at RT for 30 minutes. Sodium triacetoxyborohydride (23g) was then added and the mixture stirred at

RT overnight. The mixture was evaporated to dryness and the residue taken into water, extracted with diethyl ether (3x 200ml), the aqueous was basified to pH 9-10 and extracted with dichloromethane (3x 200ml). The dichloromethane extracts were combined, dried ($MgSO_4$) and evaporated to leave an oil (19g; same compound as Example 9 step 1). The oil was dissolved in methanol (300ml) and treated with concentrated hydrochloric acid (5ml). The mixture was stirred overnight and then evaporated to dryness to leave the title compound as the hydrochloride salt (15g).

^{1}H NMR (400MHz, DMSO-D6) δ 1.6-2.4 (m, 9H), 2.8-3.5 (m, 8H), 3.62 (m, 1H), 3.95 (s, 1H), 9.29 and 9.059 (bs, 2H), 10.9 and 11.09 (bs, 1H).

Method E

(4-Hydroxy-[1,4']bipiperidinyl-1'-yl)-(3-methanesulfonyl-phenyl)-methanone

PyBrOP™ (25.3g) was added to a stirred solution of 3-methanesulphonyl benzoic acid (10g), [1,4']bipiperidinyl-4-ol dihydrochloride (13g, see Method D) and Hunig's base (34ml) in dichloromethane (500ml). The resulting mixture was stirred at RT overnight, then washed with saturated $NaHCO_3$ solution (300ml) followed by saturated brine (300ml). The organic layer was dried ($MgSO_4$) and evaporated to leave an oily residue. Column chromatography (silica, 20% methanol in DCM) gave the product as a white solid (16g; MS: APCI$^+$(M+H) 367).

Method F

4-(3-Chloro-4-fluoro-phenoxy)-piperidine

DEAD (0.43ml) was added to a solution of triphenylphosphine (0.72g), 3-chloro-4-fluorophenol (0.403g) and 4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (0.5g) in THF at RT. The resulting mixture was stirred overnight, HCl in dioxan (2ml of 4M) was added and the mixture stirred at RT overnight. The mixture was then evaporated to dryness and triethylamine (5ml) was added. The mixture was evaporated and the residue was dissolved in methanol (10ml), placed onto a SCX cartridge (Varian, 10g, SCX cartridge available from International Sorbent Technology Isolute® Flash SCX-2) and eluted: first with methanol then with 10%NH_3 in methanol. The basic fractions were combined and evaporated to give the product as an oil (0.6g).

^{1}H NMR (299.946 MHz, DMSO-D6) δ 1.34 - 1.46 (2H, m), 1.83 - 1.91 (2H, m), 2.53 - 2.59 (2H, m), 2.87 - 2.96 (2H, m), 3.22 - 3.39 (1H, m), 4.39 (1H, septet), 6.92 - 6.98 (1H, m), 7.17 - 7.20 (1H, m), 7.30 (1H, t).

The following intermediates were prepared in similar manner to Method F:

	MS: (M+H)
4-(4-chloro-2-methyl-phenoxy)-piperidine	226
4-(4-chloro-3-fluoro-phenoxy)-piperidine	230
4-(4-chloro-2-methoxy-phenoxy)-piperidine	242
4-(4-fluoro-2-methoxy-phenoxy)-piperidine	226
4-(4-methoxy-phenoxy)-piperidine	208
4-p-tolyloxy-piperidine	192
4-(4-chloro-3-methyl-phenoxy)-piperidine	226
4-(4-chloro-phenoxy)-piperidine	212
4-(4-fluoro-phenoxy)-piperidine	196
4-(2,4-dichloro-phenoxy)-piperidine	246
4-(2-chloro-4-fluoro-phenoxy)-piperidine	230
4-(2,4-difluoro-phenoxy)-piperidine	214
4-(4-chloro-2-fluoro-phenoxy)-piperidine	230
4-(4-fluoro-2-methyl-phenoxy)-piperidine	210
4-(4-chloro-2,6-dimethyl-phenoxy)-piperidine	240
4-(2,3-dichloro-phenoxy)-piperidine	246
4-(2,5-dichloro-phenoxy)-piperidine	246
4-(2-chloro-4-methyl-phenoxy)-piperidine	226
4-(2-chloro-5-methyl-phenoxy)-piperidine	226
1-[3-methyl-4-(piperidin-4-yloxy)-phenyl]-ethanone	234
4-(2-chloro-6-methyl-phenoxy)-piperidine	226
4-[2-(piperidin-4-yloxy)-phenyl]-morpholine	263
4-(4-chloro-2-ethyl-phenoxy)-piperidine	240
7-(piperidin-4-yloxy)-quinoline	229
4-(2-tert-butyl-phenoxy)-piperidine	234
4-(indan-5-yloxy)-piperidine	218
4-(4-chloro-2-cyclohexyl-phenoxy)-piperidine	294
5-chloro-2-(piperidin-4-yloxy)-benzamide	255
4-(4-chloro-2-isoxazol-5-yl-phenoxy)-piperidine	279
4-(5-chloro-2-methyl-phenoxy)-piperidine	226
4-phenoxy-piperidine	178

4-(2,4-dichloro-6-methyl-phenoxy)-piperidine	260
4-(3-chloro-4-methyl-phenoxy)-piperidine	226
5-chloro-2-(piperidin-4-yloxy)-benzonitrile	237
4-(2,4-dichloro-3-methyl-phenoxy)-piperidine	260
4-(2-ethyl-4-fluoro-phenoxy)-piperidine	224
4-(4-methanesulfonyl-phenoxy)-piperidine	297

Method G

4-Amino-3-ethoxy-benzoic acid

Potassium hydroxide (0.278g) was added to a solution of 3-fluoro-4-nitrobenzoic acid (0.4g) in ethanol (7ml) and the reaction treated with microwaves (300W, 100°C) for 5minutes. The reaction mixture was acidified using 2N HCl and extracted with ethyl acetate. The extracts were combined, washed with water, dried ($MgSO_4$) and evaporated to give 3-ethoxy-4-nitro-benzoic acid (0.325g).

3-Ethoxy-4-nitrobenzoic acid (0.31g) was treated with 5% palladium on charcoal under an atmosphere of hydrogen (1bar) for 3hours. The reaction mixture was filtered and the filtrate was evaporated to leave the product as a beige solid (0.245g; MS: ES^- (M-H) 180).

Method H

3,4-bis-Methanesulfonyl-benzoic acid

To 3-fluoro-4-nitro-benzoic acid tert-butyl ester (0.5g) in DMSO was added $NaSO_2Me$. The reaction mixture was heated to 100°C for 24hours. A mixture of water, diethyl ether and ethyl acetate (1:1:1) was added and the resulting mixture was extracted with diethyl ether/ethyl acetate (1:1). The organic extracts were combined, dried with $MgSO_4$ and concentrated to leave a residue which was purified by chromatography (using 80% ethyl acetate/20% hexane) to give 3,4-bis-methanesulfonyl-benzoic acid tert-butyl ester (366mg). ^1H NMR (399.98 MHz, DMSO-D6) 1.59 (9H, s), 3.50 (3H, s) 3.52 (3H, s), 8.37-8.65 (3H, m).

To 3,4-bis-methanesulfonyl-benzoic acid tert-butyl ester (0.366g) in dichloromethane was added trifluoroacetic acid and the reaction mixture was stirred for 3hours. The mixture was evaporated and trituration of the residue with diethyl ether gave the title compound (0.29g; MS: $APCI^+$(M+H) 279).

Method I

4-Carbamoyl-5-methanesulfonyl-thiophene-2-carboxylic acid

To 4-cyano-5-methanesulfonyl-thiophene-2-carboxylic acid methyl ester (0.5g) in THF/H_20 (3:1; 16ml) was added LiOH (0.102g). Hydrochloric acid (2M) was added and the resulting mixture was extracted with ethyl acetate. The extracts were combined and the solvent evaporated to leave a mixture of 4-cyano-5-methanesulfonyl-thiophene-2-carboxylic acid and the title compound. This mixture was used without further purification. ^1H NMR (299.944 MHz, DMSO-D6) δ 3.62 (3H, s), 7.99 (1H, s).

Method J

3-(2-Methyl-propane-1-sulfonyl)-benzoic acid

To a suspension of 3-sulfo-benzoic acid (1g) and potassium carbonate (1.2g) in dimethylacetamide (10ml) was added iso-butyl iodide (0.65ml). The mixture was heated by microwaves (600W) at 150°C for 15 minutes. The reaction mixture was partitioned between water (100ml) and ethyl acetate (100ml), the aqueous layer was separated, acidified to pH 1 with HCl (2N) and extracted with ethyl acetate (100ml). The extract was evaporated to leave a residue which was purified by flash chromatography (Biotage 12S eluting with ethyl acetate: hexane: acetic acid, 29:70:1) to give the title product as a white solid (0.34g).

^1H NMR: (399.98 MHz, DMSO-D6) δ 0.98 (6H, d), 2.03 (1H, septet), 3.29 (2H, d), 7.81 (1H, t), 8.16 (1H, ddd), 8.27 (1H, dt), 8.38 (1H, t).

3-Cyclopropylmethanesulfonyl-benzoic acid was prepared in a similar manner to that described in Method J. MS: (M-H) 239; ^1H NMR: (DMSO-d6) δ 0.06 - 0.10 (2H, m), 0.40 - 0.45 (2H, m), 0.82 - 0.89 (1H, m), 3.34 (2H, d), 7.80 (1H, t), 8.14 (1H, d), 8.28 (1H, d), 8.39 (1H, s).

Method K

3-(2-Methoxy-ethoxy)-benzoic acid methyl ester

To a solution of methyl 3-hydroxybenzoate (5.7g) and 2-bromoethylmethyl ether (5.2g) in dimethylformamide (100ml) was added caesium carbonate (24.3g). The reaction mixture was stirred for 12 hours. The mixture was then patitioned between ethyl acetate (400ml) and water (400ml). The organic layer was separated, dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was purified by flash

chromatography (Biotage 12M, eluting iso-hexane then MeOH:dichloromethane 2:98) to give the product as a colourless oil (5.3g).

^{1}H NMR: ($CDCl_3$) δ 3.44 (3H, s), 3.75 (2H, t), 3.89 (3H, s), 4.15 (2H, t), 7.13 (1H, ddd), 7.32 (1H, t), 7.57 (1H, dd), 7.62 (1H, dt).

3-tert-Butoxycarbonylmethoxy-benzoic acid methyl ester can be prepared in a similar manner to that described in Method K: ^{1}H NMR: (299.944 MHz $CDCl_3$) 1.49 (9H, s), 3.91 (3H, s), 4.56 (2H, s), 7.13 - 7.68 (4H, m).

Method L

3-(2-Methoxy-ethoxy)-benzoic acid

To a suspention of 3-(2-methoxy-ethoxy)-benzoic acid methyl ester (5.3g) in tetrahydrofuran (200ml) was added lithium hydroxide monohydrate (5.3g) followed by water until an homogeneous solution was obtained. The reaction mixture was stirred for 12 hours, acidified and partitioned between ethyl acetate (200ml) and water (200ml). The organic layer was separated, dried ($MgSO_4$) and the solvent removed under reduced pressure to yield a colourless solid (3.6g).

^{1}H NMR: (DMSO-D6) δ 3.31 (3H, s), 3.67 (2H, t), 4.14 (2H, t), 7.20 (1H, ddd), 7.41 (1H, t), 7.44 (1H, dd), 7.53 (1H, dt)

3-(2-tert-Butoxycarbonylamino-ethoxy)-benzoic acid can be prepared in a similar manner to that described in Method L.

3-tert-Butoxycarbonylmethoxy-benzoic acid can be prepared in a similar manner to that described in Method L: ^{1}H NMR (299.944 MHz, DMSO-D6) δ 2.51 (9H, s), 4.74 (2H, s), 7.18 (1H, dq), 7.38 (1H, m), 7.41 (1H, m), 7.55 (1H, dt), 13.03 (1H, s).

Method M

4-(2-Carboxy-2-phenyl-ethyl)-piperazine-1-carboxylic acid tert-butyl ester

Piperazine-1-carboxylic acid tert-butyl ester (17.43g) and 2-phenylacrylic acid (18g) in iso-propanol (500ml) was heated at reflux for four days. The resulting precipitate was filtered, washed with diethyl ether and dried under vacuum to give the title compound as a white solid (17g; MS: $APCI^+$(M+H) 335).

Method N

5-Methanesulfonyl-1H-indole-2-carboxylic acid

To a solution of the 5-methanesulfonyl-1H-indole-2-carboxylic acid methyl ester (0.49g) in THF (12mL) and water (4ml) was added LiOH (0.098g). The reaction mixture was left to stir for 2hours. Acetic acid was added and the product extracted with

dichloromethane. The organic extracts were combined, dried with magnesium sulfate, filtered and the filtrate evaporated to give the title compound as a solid (0.110g).

^{1}H NMR (299.946 MHz, DMSO-D6) δ 3.18 (3H, s), 7.32 - 7.33 (1H, m), 7.61 - 7.64 (1H, m), 7.73 - 7.77 (1H, m), 8.30 - 8.31 (1H, m).

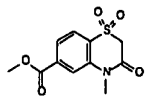
Method O

5-Methyl-imidazo[1,2-a]pyridine-2-carboxylic acid was prepared in a similar manner to 6-fluoro-imidazo[1,2-a]pyridine-2-carboxylic acid (see Example 25) using the commercially available 5-methyl-1,8a-dihydro-imidazo[1,2-a]pyridine-2-carboxylic acid ethyl ester. 6-Methyl-imidazo[1,2-a]pyridine-2-carboxylic acid and 6-methyl-imidazo[1,2-a]pyridine-2-carboxylic acid ethyl ester were prepared in a similar manner to 6-fluoro-imidazo[1,2-a]pyridine-2-carboxylic acid and its ester above.

Method P

Preparation of 4-Methyl-1,1,3-trioxo-1,2,3,4-tetrahydro-1λ^6-benzo[1,4]thiazine-6-carboxylic acid

Step 1: 4-Methyl-1,1,3-trioxo-1,2,3,4-tetrahydro-1λ^6-benzo[1,4]thiazine-6-carboxylic acid methyl ester



To a solution of 4-methyl-3-oxo-3,4-dihydro-2H-benzo[1,4]thiazine-6-carboxylic acid methyl ester (1g) in dichloromethane (25ml) was added 32% peracetic acid dropwise over 10minutes. The reaction mixture was stirred at room temperature for 48hours and then diluted with dichloromethane. The organic phase was washed once with water, twice with aqueous sodium sulfite solution, and once with saturated aqueous sodium bicarbonate. The organic phase was dried over magnesium sulfate, filtered, and the solvent evaporated to give the sub-title compound as a solid (1.012g).

^{1}H NMR (399.978 MHz, $CDCl_3$) δ 3.58 (3H, s), 4.00 (3H, s), 4.27 (2H, s), 7.96 - 7.99 (2H, m), 8.04 - 8.06 (1H, m).

Step 2: 4-Methyl-1,1,3-trioxo-1,2,3,4-tetrahydro-1λ^6-benzo[1,4]thiazine-6-carboxylic acid

To a solution of 4-methyl-1,1,3-trioxo-1,2,3,4-tetrahydro-11 6-benzo[1,4]thiazine-6-carboxylic acid methyl ester (1g, from step 1) in MeOH (7ml) was added dropwise a

solution of sodium hydroxide (0.6g) in water (5ml). The reaction mixture was stirred at room temperature for 1hour, diluted with water, cooled in an ice/water bath. Slow acidification with HCl (1N) to pH 2 yielded a precipitate which was isolated by filtration to give the title compound (0.595g) as a solid.

^{1}H NMR (399.978MHz, DMSO-D6) δ 3.49 (3H,s), 4.91 (2H,s), 7.90-8.03 (3H,m).

Method Q

Preparation of 4-(4-methanesulfonyl-phenoxy)-[1,4']bipiperidinyl

Step a: 4-(4-methanesulfonyl-phenoxy)-[1,4']bipiperidinyl-1'-carboxylic acid tert-butyl ester

To a solution of 4-(4-methanesulfonyl-phenoxy)-piperidine (0.7g) dissolved in THF (5ml) and 1,2-dichloroethane (10ml) with 1-Boc-4-piperidone (0.71g) was added $NaBH(OAc)_3$ (0.926g) and acetic acid (0.18g). After 16hours at RT aqueous NaOH (1M) solution and dichloromethane were added and the mixture was extracted with dichloromethane. The combined organic extracts were washed with water, dried with magnesium sulfate and concentrated to leave a residue which was purified by chromatography (dichloromethane : methanol 90:10) to give the sub-title product (1.1g; MS: $APCI^+$(M+H) 439).

Step b: 4-(4-methanesulfonyl-phenoxy)-[1,4']bipiperidinyl

The product of step a was dissolved in dichloromethane (20ml) and trifluoroacetic acid (5ml) was added. After 16hours at room temperature the solution was evaporated to leave the title compound as a TFA salt. The free base (0.7g; oil; MS: $APCI^+$(M+H) 339) was liberated by addition of aqueous NaOH (1M) and extraction with dichloromethane followed by evaporation of the solvent.

3-Methanesulfonyl-5-nitro-benzoic acid and 3-cyano-5-methanesulfonyl-benzoic acid can be prepared according to a method described in EP-A1-556674.

2-amino-5-$MeSO_2$-benzoic acid can be prepared according to a method described in J. Org. Chem. (1953) 18 1380.

3-Ethanesulfonyl-benzoic acid can be prepared according to a method described in J. Chem. Soc. 1946, 763.

3-Methylsulfamoyl-benzoic acid and 3-dimethylsulfamoyl-benzoic acid can be prepared according to a method described in DE2133038. 3-Methylsulfamoyl-benzoic

acid ^{1}H NMR: (399.98 MHz, DMSO-D6) δ 7.42 (3H, d), 7.63 (1H, q), 7.76 (1H, t), 8.01 (1H, m), 8.18 (1H, dt), 8.31 (1H, t), 13.48 (1H, s).

Other intermediates can be prepared by literature methods, by adaptation of literature methods or are available commercially. For example:

- (2-methyl-4-nitro-2H-pyrazol-3-yl)methanecarboxylic acid, 2-{1-[sulfonyl chloride]-ethyl}-isoindole-1,3-dione and (1,3-dimethyl-3,7-dihydro-purine-2,6-dion-8-yl)methanecarboxylic acid are available from Salor (Aldrich Chemical Company Inc 1001 West Saint Paul Avenue Milwaukee, WI 53233 USA);
- [4-amino-5-(iso-propyl-sulfonyl)-thiophen-3-yl]carboxylic acid, [3-methyl-5-(4-methyl-[1,2,3]thiadiazol-5-yl)-isoxazol-4-yl]carboxylic acid, 3-cyano-4-(pyrrol-1-yl)-thiophen-5-yl)carboxylic acid, 4-isopropylsulfanyl-1,3-dimethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid and 1-cyclopropyl-5-methoxy-2-methyl-2,3-dihydro-1H-indole-3-carboxylic acid, (5-(isoxazol-3-yl)-thiophen-2-yl)sulfonyl chloride, 4-bromo-1-methyl-1H-pyrazol-3-ylmethanal, 4-chloro-1H-pyrazol-3-ylmethanal and 1-(4-chloro-benzyl)-1H-pyrazol-3-ylmethanal are available from Maybridge Chemical Company Ltd.; Trevillett, Tintagel, Cornwall PL34 0HW, UK;
- (5-methanesulfonyl-1H-indol-2-yl)carboxylic acid is available by hydrolysis of an ester available from Maybridge Chemical Company Ltd., details above;
- (4-chloro-5-methyl-3-nitro-pyrazol-1-yl)methanecarboxylic acid, (5-methyl-3,4-dinitro-pyrazol-1-yl)methanecarboxylic acid and (2,4-dinitro-imidazol-1-yl)methanecarboxylic acid are available from ASINEX Ltd., 6 Schukinskaya ulitsa, Moscow 123182, Russia;
- (6-(imidazol-1-yl)-pyridin-3-yl)carboxylic acid and 2-methyl-2-([1,2,4]triazol-1-yl)-propanoic acid are available from Bionet Research Ltd, 3 Highfield Industrial Estate, Camelford, Cornwall PL32 9QZ, UK; and,
- (2-methyl-[1,8]naphthyridin-3-yl)carboxylic acid, (2-methyl-[1,6]naphthyridin-3-yl)carboxylic acid and (5-trifluoromethyl-thieno[3,2-b]pyridin-6-yl)-methanecarboxylic acid are available from Peakdale Fine Chemicals Ltd., 7 Brookfield Industrial Estate, Glossop, Derbyshire, SK13 6LQ, UK.

Example 28

Pharmacological Analysis: Calcium flux $[Ca^{2+}]_i$ assay

Human eosinophils

Human eosinophils were isolated from EDTA anticoagulated peripheral blood as previously described (Hansel et al., *J. Immunol. Methods*, 1991, 145, 105-110). The cells were resuspended ($5x10^6$ ml^{-1}) and loaded with 5μM FLUO-3/AM + Pluronic F127 2.2μl/ml (Molecular Probes) in low potassium solution (LKS; NaCl 118mM, $MgSO_4$ 0.8mM, glucose 5.5mM, Na_2CO_3 8.5mM, KCl 5mM, HEPES 20mM, $CaCl_2$ 1.8mM, BSA 0.1%, pH 7.4) for one hour at room temperature. After loading, cells were centrifuged at 200g for 5min and resuspended in LKS at $2.5x10^6$ ml^{-1}. The cells were then transferred to 96 well FLIPr plates (Poly-D-Lysine plates from Becton Dickinson pre-incubated with 5μM fibronectin for two hours) at 25μl/well. The plate was centrifuged at 200g for 5min and the cells were washed twice with LKS (200μl; room temperature).

A compound of the Examples was pre-dissolved in DMSO and added to a final concentration of 0.1%(v/v) DMSO. Assays were initiated by the addition of an A_{50} concentration of eotaxin and the transient increase in fluo-3 fluorescence (l_{Ex} =490nm and l_{Em} = 520nm) monitored using a FLIPR (Fluorometric Imaging Plate Reader, Molecular Devices, Sunnyvale, U.S.A.).

Human eosinophil chemotaxis

Human eosinophils were isolated from EDTA anticoagulated peripheral blood as previously described (Hansel et al., *J. Immunol. Methods*, 1991, 145, 105-110). The cells were resuspended at $10x10^6$ ml^{-1} in RPMI containing 200 IU/ml penicillin, 200 μg/ml streptomycin sulphate and supplemented with 10% HIFCS, at room temperature.

Eosinophils (700 μl) were pre-incubated for 15 mins at 37° C with 7 μl of either vehicle or compound (100x required final concentration in 10% DMSO). The chemotaxis plate (ChemoTx, 3μm pore, Neuroprobe) was loaded by adding 28μl of a concentration of eotaxin (0.1 to 100nM) containing a concentration of a compound according to the Examples or solvent to the lower wells of the chemotaxis plate. The filter was then placed over the wells and 25 μl of eosinophil suspension were added to the top of the filter. The plate was incubated for 1 hr at 37° C in a humidified incubator with a 95% air/5% CO_2 atmosphere to allow chemotaxis.

The medium, containing cells that had not migrated, was carefully aspirated from above the filter and discarded. The filter was washed once with phosphate buffered saline (PBS) containing 5 mM EDTA to remove any adherent cells. Cells that had migrated through the filter were pelleted by centrifugation (300xg for 5 mins at room temperature) and the filter removed and the supernatant transferred to each well of a 96-well plate (Costar). The pelleted cells were lysed by the addition of 28 μl of PBS containing 0.5% Triton x100 followed by two cycles of freeze/thawing. The cell lysate was then added to the supernatant. The number of eosinophils migrating was quantified according to the method of Strath et al., *J. Immunol. Methods*, 1985, 83, 209 by measuring eosinophil peroxidase activity in the supernatant.

Compounds of the Examples were found to be antagonists of the eotaxin mediated human eosinophil chemotaxis.

Example 29

Guinea-pig isolated trachea

(See for example, Harrison, R.W.S., Carswell, H. & Young, J.M. (1984) European J. Pharmacol., 106, 405-409.)

Male albino Dunkin-Hartley guinea-pigs (250g) were killed by cervical dislocation and the whole trachea removed. After clearing the adherent connective tissue, the trachea was cut into six ring segments each three cartilage bands wide and then suspended in 20ml organ baths containing Krebs-Henseleit solution of the following composition (mM): NaCl 117.6, NaH_2PO_4 0.9, $NaHCO_3$ 25.0, $MgSO_4$ 1.2, KCl 5.4, $CaCl_2$ 2.6 and glucose 11.1. The buffer was maintained at 37°C and gassed with 5% CO_2 in oxygen. Indomethacin (2.8μM) was added to the Krebs solution to prevent development of smooth muscle tone due to the synthesis of cyclo-oxygenase products. The tracheal rings were suspended between two parallel tungsten wire hooks, one attached to an Ormed beam isometric force transducer and the other to a stationary support in the organ bath. Changes in isometric force were recorded on 2-channel Sekonic flat bed chart recorders.

Experimental protocols

At the beginning of each experiment a force of 1g was applied to the tissues and this was reinstated over a 60 minute equilibration period until a steady resting tone was achieved. Subsequently, a cumulative histamine concentration effect (E/[A]) curve was constructed at 0.5 log_{10} unit increments, in each tissue. The tissues were then washed and approximately 30

minutes later, test compound or vehicle (20% DMSO) was added. Following an incubation period of 60 minutes a second E/[A] curve was performed to histamine.

Contraction responses were recorded as a percentage of the first curve maximum.

Data analysis

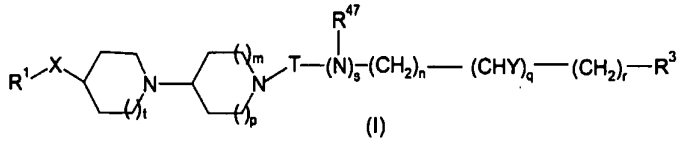
Experimental E/[A] curve data were analysed for the purposes of estimating the potencies ($p[A_{50}]$ values) of histamine in the absence and presence of the test compound. Affinity (pA_2) values of test compounds were subsequently calculated using the following equation:

$$\log(r-1) = \log[B] + pA_2$$

where $r = [A]_{50}$ in presence of test compound/$[A]_{50}$ in absence of antagonist and [B] is the concentration of test compound. Compounds of the Examples were found to be H1 antagonists.

CLAIMS

1. A compound of formula (I):



(I)

wherein:

q, s and t are, independently, 0 or 1;

n and r are, independently, 0, 1, 2, 3, 4 or 5;

m and p are, independently, 0, 1 or 2;

X is CH_2, C(O), O, S, S(O), $S(O)_2$ or NR^{37}; provided that when m and p are both 1 then X is not CH_2;

Y is NHR^2 or OH;

T is C(O), C(S), $S(O)_2$ or CH_2;

R^1 is hydrogen, C_{1-6} alkyl, aryl or heterocyclyl;

R^2 and R^{47} are, independently, hydrogen, C_{1-6} alkyl, aryl(C_{1-4})alkyl or CO(C_{1-6} alkyl);

R^3 is C_{1-6} alkyl {optionally substituted by halogen, CO_2R^4 or phthalimide}, $CR^{3a}R^{3b}R^{3c}$, C_{2-4} alkenyl {optionally substituted by aryl or heterocyclyl}, C_{3-7} cycloalkyl {optionally substituted by C_{1-4} alkyl, aryl or oxo}, C_{3-7} cycloalkenyl {optionally substituted by oxo, C_{1-6} alkyl or aryl}, aryl, heterocyclyl, thioaryl or thioheterocyclyl;

R^{3a} is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy or C_{3-7} cycloalkyl; R^{3b} is aryl, heterocyclyl, $S(O)_2$aryl or $S(O)_2$heterocyclyl; and R^{3c} is C_{1-6} alkyl, C_{1-4} haloalkyl, hydroxy, heterocyclyl(C_{1-4} alkyl) or aryl;

wherein, unless stated otherwise, the foregoing aryl and heterocyclyl moieties are optionally substituted by: halogen, OH, SH, NO_2, oxo, C_{1-6} alkyl {itself optionally substituted by halogen, $OC(O)C_{1-6}$ alkyl, $S(O)_2R^{48}$, phenyl (itself optionally substituted by halogen (such as one or two chlorine or fluorine atoms), C_{1-6} alkyl, $S(O)_2R^{38}$ or $C(O)NR^{39}R^{40}$), naphthyloxy (itself optionally substituted by halo or C_{2-6} alkenyl), C_{3-10} cycloalkyl (itself optionally substituted by C_{1-4} alkyl or oxo) or $NR^{41}C(O)OCH_2$(fluoren-9-yl)}, $NR^{41}C(O)OCH_2$(fluoren-9-yl), C_{1-6} alkoxy {itself

optionally substituted by halogen, C_{1-6} alkoxy, $NHCO_2(C_{1-6}$ alkyl), CO_2R^4, NR^5R^6 or phenyl (itself optionally substituted by halogen or NO_2)}, C_{1-6} alkylthio, C_{1-6} haloalkylthio, C_{3-10} cycloalkyl, NR^7R^8, $NR^9C(O)R^{10}$, CO_2R^{11}, $C(O)NR^{12}R^{13}$, $C(O)R^{14}$, $S(O)_dR^{15}$, $S(O)_2NR^{42}R^{43}$, $NR^{44}S(O)_2R^{45}$, phenyl {itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy (itself optionally substituted by halogen, OH or pyridinyl), phenyl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy) or heterocyclyl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy)}, heterocyclyl {itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy, C_{1-6} haloalkoxy, phenyl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy) or heterocyclyl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy)}, phenoxy {itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy, C_{1-6} haloalkoxy, phenyl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy) or heterocyclyl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy)}, SCN, CN, SO_3H (or an alkali metal salt thereof), methylenedioxy or difluoromethylenedioxy; when aryl is phenyl adjacent substituents may join to form, together with the phenyl ring to which they are attached, a dihydrophenanthrene moiety;

d is 0, 1 or 2;

R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{37}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43} and R^{44} are, independently, hydrogen, C_{1-6} alkyl, aryl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy) or heterocyclyl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy);

R^{15}, R^{38}, R^{45} and R^{48} are, independently, C_{1-6} alkyl (optionally substituted by halogen, hydroxy or C_{3-10} cycloalkyl), C_{3-6} alkenyl, aryl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy) or heterocyclyl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy);

or an N-oxide thereof; or a pharmaceutically acceptable salt thereof; or a solvate thereof; provided that:

when m and p are both 1, n, q and r are all 0, T and X are both $S(O)_2$, and R^1 is methoxyphenyl then R^3 is not propyl; when m, p, q and r are all 1, n is 0, Y is NH_2, T is CO and R^1X is $(CH_3)_2N$ then R^3 is not 3,5-dibromo-4-aminophenyl, 1-methylindol-3-yl or 1-(tert-butoxycarbonyl)indol-3-yl; and when m and p are both 1, n, q and r are all 0, T is CO, X is NH and R^1 is 3-(4-fluorobenzyl)benzimidazol-2-yl then R^3 is not 4-fluorophenyl.

2. A compound as claimed in claim 1 wherein aryl is phenyl or naphthyl.

3. A compound as claimed in claim 1 or 2 wherein heterocyclyl is furyl, thienyl, pyrrolyl, 2,5-dihydropyrrolyl, thiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, piperidinyl, morpholinyl, pyridinyl, pyrimidinyl, indolyl, 2,3-dihydroindolyl, benzo[b]furyl, benz[b]thienyl, 2,3-dihydrobenz[b]thienyl, indazolyl, benzimidazolyl, benztriazolyl, benzoxazolyl, benzthiazolyl, 2,3-dihydrobenzthiazolyl, 1,2,3-benzothiadiazolyl, imidazo[1,2a]pyridinyl, thieno[3,2-b]pyridin-6-yl 1,2,3-benzoxadiazolyl, 2,1,3-benzothiadiazolyl, benzofurazan, quinoxalinyl, dihydro-1-benzopyryliumyl, 3,4-dihydro-1H-2,1-benzothiazinyl, a pyrazolopyridine, a purine, quinolinyl, isoquinolinyl, a naphthyridinyl, a benzothiazinyl, benzo[d]imidazo[2,1-b]thiazol-2-yl or dibenzothiophenyl; or an N-oxide thereof, or an S-oxide or S-dioxide thereof.

4. A compound as claimed in claim 1, 2 or 3 wherein the variables m and p are such that m + p is 0, 1 or 2.

5. A compound as claimed in any one of the preceding claims wherein n is 0 or 1.

6. A compound as claimed in any one of the preceding claims wherein q and r are both 0.

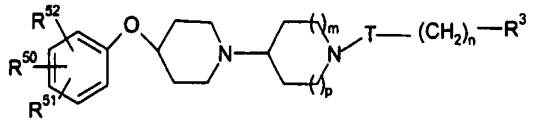
7. A compound as claimed in any one of the preceding claims wherein m, p and t are all 1.

8. A compound as claimed in any one of the preceding claims wherein s is 0.

9. A compound as claimed in any one of the preceding claims wherein X is O.

10. A compound as claimed in any one of the preceding claims wherein R^1 is phenyl substituted with one or more of fluorine, chlorine, C_{1-4} alkyl or C_{1-4} alkoxy.

11. A compound of formula (Ia"):



(Ia")

wherein:

T is C(O), C(S), $S(O)_2$ or CH_2;

n is 0, 1, 2, 3, 4 or 5;

m and p are, independently, 0, 1 or 2 (but are especially both 1);

R^{50} is hydrogen, cyano, $S(O)_2(C_{1-4}$ alkyl), $S(O)_2(C_{1-4}$ haloalkyl), halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy or phenyl (optionally substituted by one or two halogen atoms or by one $C(O)NR^{12'}R^{13'}$, $NR^{9'}C(O)R^{10'}$, $S(O)_2R^{15'}$, $S(O)_2NR^{42}R^{43}$ or $NR^{44}S(O)_2R^{45}$ group);

R^{51} and R^{52} are, independently, hydrogen, halogen, C_{1-4} alkyl or C_{1-4} alkoxy;

R^3 is C_{1-6} alkyl {optionally substituted by halogen, CO_2R^4 or phthalimide}, C_{3-7} cycloalkyl {optionally substituted by C_{1-4} alkyl or oxo}, aryl or heterocyclyl;

wherein, unless stated otherwise, the foregoing aryl and heterocyclyl moieties are optionally substituted by: halogen, OH, SH, NO_2, oxo, C_{1-6} alkyl (itself optionally substituted by halogen, $OC(O)C_{1-6}$ alkyl, phenyl (itself optionally substituted by halo or C_{1-6} alkyl), naphthyloxy (itself optionally substituted by halo or C_{2-6} alkenyl) or $NR^4C(O)OCH_2$(fluoren-9-yl)), C_{1-6} alkoxy (itself optionally substituted by halogen, CO_2R^4, NR^5R^6 or phenyl (itself optionally substituted by halogen or NO_2)), C_{1-6} alkylthio, nitro, C_{3-7} cycloalkyl, NR^7R^8, $NR^9C(O)R^{10}$, CO_2R^{11}, $C(O)NR^{12}R^{13}$, $C(O)R^{14}$, $S(O)_2R^{15}$, phenyl (itself optionally substituted by NO_2 or C_{1-6} alkoxy (itself optionally substituted by OH or pyridinyl)), phenoxy, SCN, CN,

SO_3H (or an alkali metal salt thereof) or methylenedioxy; when aryl is phenyl adjacent substituents may join to form, together with the phenyl ring a dihydrophenanthrene moiety;

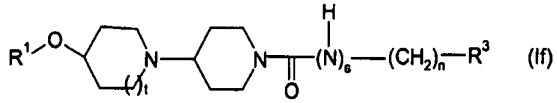
R^4, R^5, R^6, R^7, R^8, R^9, $R^{9'}$, R^{10}, $R^{10'}$, R^{11}, R^{12}, $R^{12'}$, R^{13}, $R^{13'}$, R^{14}, R^{42}, R^{43} and R^{44} are, independently, hydrogen, C_{1-6} alkyl or phenyl;

R^{15}, $R^{15'}$ and R^{45} are, independently, C_{1-6} alkyl or phenyl;

or a pharmaceutically acceptable salt thereof.

12. A compound as claimed in any one of the preceding claims wherein T is C(O), $S(O)_2$ or CH_2.

13. A compound of formula (If):



(If)

wherein R^1, n, t, s and R^3 are as defined in claim 1.

14. A compound as claimed in any one of the preceding claims wherein R^3 is aryl or heteroaryl either of which is optionally substituted as described in claim 1.

15. A compound as claimed in any one of the preceding claims wherein R^3 is phenyl or heterocyclyl, either of which is optionally substituted by: halo, hydroxy, nitro, cyano, amino, C_{1-4} alkyl (itself optionally substituted by $S(O)_2(C_{1-4}$ alkyl), $S(O)_2$phenyl), C_{1-4} alkoxy, $S(O)_kR^{46}$ (wherein k is 0, 1 or 2; and R^{46} is C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{3-7} cycloalkyl(C_{1-4} alkyl) or phenyl), C_{1-4} haloalkylthio, $C(O)NH_2$, $NHS(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl) or $S(O)_2N(C_{1-4}$ alkyl)$_2$.

16. A compound as claimed in claim 11 wherein m and p are both 1.

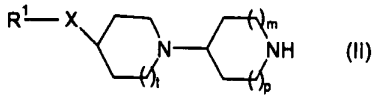
17. A compound as claimed in claim 11 or claim 13 wherein n is 0 or 1.

18. A compound as claimed in claim 13 wherein R^1 is phenyl substituted with one or more of fluorine, chlorine, C_{1-4} alkyl or C_{1-4} alkoxy.

19. A compound as claimed in claim 13 wherein s is 0 and t is 1.

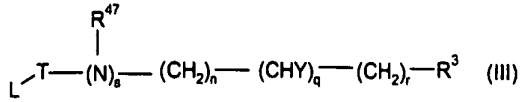
20. A process for preparing a compound of formula (I) as claimed in claim 1, which comprises:

a) when R^{47} is not hydrogen, coupling a compound of formula (II):



(II)

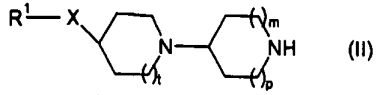
with a compound of formula (III):



(III)

wherein L is a suitable leaving group, and the variables Y and T are optionally protected during the course of the reaction;

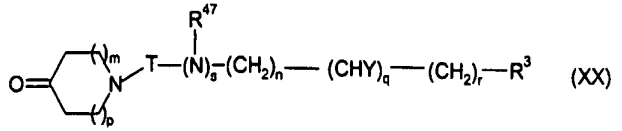
b) when s is 1, R^{47} is hydrogen and T is CO, reacting a compound of formula (II):



(II)

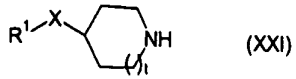
with an isocyanate $O=C=N-(CH_2)_n-(CH_2)_r-R^3$;

c) reductively aminating of a compound of formula (XX):



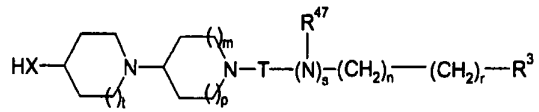
(XX)

with an amine of formula (XXI):



(XXI)

d) performing a fluoride displacement reaction on F-R^1 in the presence of compound of formula (XVIII):



(XVIII)

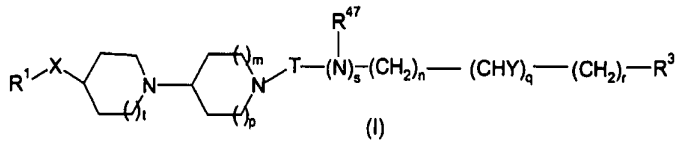
provided that R^{47} is not hydrogen.

21. A pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt thereof or a solvate thereof, and a pharmaceutically acceptable adjuvant, diluent or carrier.

22. A compound of the formula (I) as claimed in claim 1, or a pharmaceutically acceptable salt thereof or a solvate thereof, for use as a medicament.

23. The use of a compound of the formula (I) as claimed in claim 1, or a pharmaceutically acceptable salt thereof or a solvate thereof, in the manufacture of a medicament for use in therapy.

24. The use of a compound of a formula (I):



(I)

wherein:

q, s and t are, independently, 0 or 1;

n and r are, independently, 0, 1, 2, 3, 4 or 5;

m and p are, independently, 0, 1 or 2;

X is CH_2, C(O), O, S, S(O), $S(O)_2$ or NR^{37}; provided that when m and p are both 1 then X is not CH_2;

Y is NHR^2 or OH;

T is C(O), C(S), $S(O)_2$ or CH_2;

R^1 is hydrogen, C_{1-6} alkyl, aryl or heterocyclyl;

R^2 and R^{47} are, independently, hydrogen, C_{1-6} alkyl, aryl(C_{1-4})alkyl or CO(C_{1-6} alkyl);

R^3 is C_{1-6} alkyl {optionally substituted by halogen, CO_2R^4 or phthalimide}, $CR^{3a}R^{3b}R^{3c}$, C_{2-4} alkenyl {optionally substituted by aryl or heterocyclyl}, C_{3-7} cycloalkyl {optionally substituted by C_{1-4} alkyl, aryl or oxo}, C_{3-7} cycloalkenyl {optionally substituted by oxo, C_{1-6} alkyl or aryl}, aryl, heterocyclyl, thioaryl or thioheterocyclyl;

R^{3a} is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy or C_{3-7} cycloalkyl; R^{3b} is aryl, heterocyclyl, $S(O)_2$aryl or $S(O)_2$heterocyclyl; and R^{3c} is C_{1-6} alkyl, C_{1-4} haloalkyl, hydroxy, heterocyclyl(C_{1-4} alkyl) or aryl;

wherein, unless stated otherwise, the foregoing aryl and heterocyclyl moieties are optionally substituted by: halogen, OH, SH, NO_2, oxo, C_{1-6} alkyl {itself optionally substituted by halogen, $OC(O)C_{1-6}$ alkyl, $S(O)_2R^{48}$, phenyl (itself optionally substituted by halogen (such as one or two chlorine or fluorine atoms), C_{1-6} alkyl, $S(O)_2R^{38}$ or $C(O)NR^{39}R^{40}$), naphthyloxy (itself optionally substituted by halo or C_{2-6} alkenyl), C_{3-10} cycloalkyl (itself optionally substituted by C_{1-4} alkyl or oxo) or $NR^{41}C(O)OCH_2$(fluoren-9-yl)}, $NR^{41}C(O)OCH_2$(fluoren-9-yl), C_{1-6} alkoxy {itself optionally substituted by halogen, C_{1-6} alkoxy, $NHCO_2(C_{1-6}$ alkyl), CO_2R^4, NR^5R^6 or phenyl (itself optionally substituted by halogen or NO_2)}, C_{1-6} alkylthio, C_{1-6} haloalkylthio, C_{3-10} cycloalkyl, NR^7R^8, $NR^9C(O)R^{10}$, CO_2R^{11}, $C(O)NR^{12}R^{13}$, $C(O)R^{14}$, $S(O)_dR^{15}$, $S(O)_2NR^{42}R^{43}$, $NR^{44}S(O)_2R^{45}$, phenyl {itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy (itself optionally substituted by halogen, OH or pyridinyl), phenyl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy) or heterocyclyl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy)}, heterocyclyl {itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy, C_{1-6} haloalkoxy, phenyl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy) or heterocyclyl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy)}, phenoxy {itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy, C_{1-6} haloalkoxy, phenyl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy) or heterocyclyl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy)}, SCN, CN, SO_3H (or an alkali

metal salt thereof), methylenedioxy or difluoromethylenedioxy; when aryl is phenyl adjacent substituents may join to form, together with the phenyl ring to which they are attached, a dihydrophenanthrene moiety;

d is 0, 1 or 2;

R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{37}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43} and R^{44} are, independently, hydrogen, C_{1-6} alkyl, aryl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy) or heterocyclyl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy);

R^{15}, R^{38}, R^{45} and R^{48} are, independently, C_{1-6} alkyl (optionally substituted by halogen, hydroxy or C_{3-10} cycloalkyl), C_{3-6} alkenyl, aryl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy) or heterocyclyl (itself optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, C_{1-6} alkoxy or C_{1-6} haloalkoxy);

or an N-oxide thereof; or a pharmaceutically acceptable salt thereof; or a solvate thereof; in the manufacture of a medicament for use in modulating chemokine receptor activity or H1 antagonising activity in a warm blooded animal.

25. A compound of a formula (I), as defined in claim 24, which is both a modulator of chemokine receptor activity and an H1 antagonist.

26. Method of treating a CCR3 mediated disease state comprising administering to a patient an effective amount of a compound of formula (I) as defined in claim 24.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/00751

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 401/04, C07D 409/14, C07D 417/14, A61K 31/445, A61P 37/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5977138 A (WANG ET AL), 2 November 1999 (02.11.99), the claims and examples	1-10,12-15, 18-23,25
X	WO 9806697 A1 (SCHERING CORPORATION), 19 February 1998 (19.02.98), the claims and examples	1-10,12-15, 18-23,25
X	EP 0151826 A1 (JANSSEN PHARMACEUTICA N.V.), 21 August 1985 (21.08.85), the claims, page 1, lines 29-30	1-25

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 August 2001	22 -08- 2001
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Solveig Gustavsson/BS Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/00751

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0151824 A2 (JANSSEN PHARMACEUTICA N.V.), 21 August 1985 (21.08.85), the claims, compound 36, example 30, page 22, line 25	1-25
X	EP 0145037 A2 (JANSSEN PHARMACEUTICA N.V.), 19 June 1985 (19.06.85), the claims, page 1, line 31	1-25
X	EP 0099139 A2 (JANSSEN PHARMACEUTICA N.V.), 25 January 1984 (25.01.84), the claims, page 1, lines 10-11	1-25
X	US 4695575 A (JANSSENS ET AL), 22 Sept 1987 (22.09.87), the claims, example 51, column 1, lines 30-31	1-25
X	WO 9805292 A2 (SCHERING CORPORATION), 12 February 1998 (12.02.98), the claims, examples 448, 489 and 493, page 133	1-8,12,20-23
X	WO 9634857 A1 (SCHERING CORPORATION), 7 November 1996 (07.11.96), formula step 1, page 37	1-2,4-6,8-9, 12,14-15
X	WO 9811128 A1 (DR. KARL THOMAE GMBH), 19 March 1998 (19.03.98), the claims, the description pages 179-197, examples A22 (p 236), A31 (p 252 and 254) and A32 (p 254 and 258)	1-8,12,21-23

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/00751

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 26
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
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Claim 26 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT
Information on patent family members

02/07/01

International application No.
PCT/SE 01/00751

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International application No.
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International application No.
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